The Journal of
CLINICAL ENDOCRINOLOGY
AND METABOLISM

VOLUME 17 DECEMBER, 1957 NUMBER 12
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METABOLISM OF FREE AND CONJUGATED 17-HYDROXYCORTICOSTEROIDS IN SUBJECTS WITH LIVER DISEASE*

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INTRODUCTION

A PREVIOUS report from this laboratory (1) demonstrated a delay in the removal of cortisol but not of tetrahydrocortisone (Tetra E) from the plasma of subjects with liver disease. Since Tetra E glucuronide is one of the principal end-products of cortisol metabolism (2), it was felt that the impaired removal of cortisol in subjects with liver disease was attributable to a block in the degradation of cortisol to its reduction products rather than to an impairment of conjugation of the reduced 17-hydroxycorticosteroids (17-OHCS). With the development of methods for the measurement of 17-OHCS conjugated with glucuronic acid in body fluids (3, 4), subnormal levels of conjugated 17-OHCS in the plasma of subjects with liver disease after the ingestion of cortisone were noted in other lab-

Received March 21, 1957.

* Some aspects of this study appeared in an abstract in the Proceedings of the American Society for Clinical Investigation (*J. Clin. Invest.* **34**: 924 (June) 1955). The data in this paper were included in a presentation at the Seventh Annual Meeting of the American Association for the Study of Liver Diseases, Chicago, Illinois, November 8, 1956.

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oratories. These findings were thought to be a result of a diminished capacity to conjugate 17-OHCS in subjects with hepatic disorders (5, 6).

In the present study the levels of free and conjugated 17-OHCS in the plasma of patients with cirrhosis of the liver have been measured after the administration of cortisol and certain of its degradation products, with a twofold purpose: first, to determine whether or not there was diminished conjugation of 17-OHCS in the presence of suitable substrate; and second, to ascertain whether or not the metabolic pathway of cortisol degradation might be deduced from the pattern of conjugated 17-OHCS concentrations in the plasma after infusions of the reduction products of cortisol.

MATERIALS AND METHODS

The subjects in the study were hospitalized patients with clinical and laboratory evidence of severe liver disease. Most of them had portal cirrhosis, but 3 had viral hepatitis, 1 had metastatic carcinoma of the liver, 1 had postnecrotic cirrhosis, and 1 had cirrhosis and a portacaval shunt. Liver function was evaluated in each subject by the usual liver function tests, but particular attention was paid to bromsulphalein (BSP) retention forty-five minutes after an intravenous dose of 5 mg. per Kg. of body weight. The presence or absence of ascites was carefully noted in each patient. Renal function was evaluated by measurement of the 24-hour endogenous creatinine clearance.

A standard cortisol infusion (1 mg. per Kg.) was administered on 26 occasions to 21 subjects and blood samples for determination of the levels of free and conjugated 17-OHCS in the plasma were drawn at 0, 0.5, 1, 2, 4 and 6 hours after the beginning of the infusion, which lasted about thirty minutes. The standard infusion protocol has been described (1).

Nine subjects received an intravenous infusion of tetrahydrocortisone (Tetra E) over a 30-minute period according to published methods (1); 4 received tetrahydrocortisol (Tetra F), and 8 received dihydrocortisone (Di E) in a similar manner. Serial samples of blood for the estimation of free and conjugated 17-OHCS levels in the plasma were drawn over a six-hour period. Four subjects received an infusion of Tetra E, 3 an infusion of Tetra F, and 3 an infusion of Di E, administered within five minutes (7).

One subject, A.S., was given a 30-minute infusion of Tetra F, after which samples of blood and ascitic fluid for the estimation of conjugated 17-OHCS were drawn during the subsequent twenty-four hours.

The levels of free 17-OHCS in the plasma were measured by the method of Nelson, Samuels and Eik-Nes (8, 9), and of conjugated 17-OHCS by a modification (7) of the technique of Bongiovanni (3).

RESULTS

Free and conjugated 17-OHCS in plasma after infusion of cortisol

The levels of free and conjugated 17-OHCS in the plasma following infusion of cortisol are summarized in Table 1, and the mean values are plotted in Figure 1 and Figure 3. When the logarithms of the plasma levels of free 17-OHCS were plotted against time, the points fell on a straight line after the one-hour value. The slope of this line was -0.092 and the half-life of cortisol disappearance was 229 ± 19 (standard error of the

TABLE 1. EFFECT OF CORTISOL INFUSIONS ON PLASMA 17-OHCS LEVELS

Patient	Age, Sex	Diagnosis	BSP (% retention)	Creatinine clearance (ml./min.)	Plasma 17-OHCS Levels (γ/100 ml.) 0 hr. F	0 hr. C	0.5 hr. F	0.5 hr. C	1 hr. F	1 hr. C	2 hrs. F	2 hrs. C	4 hrs. F	4 hrs. C	6 hrs. F	6 hrs. C	Half-life (min.)
Liver Disease without Ascites																	
L.C.	23, M	Hepatitis	26		14				81		61		38		21		156
C.P.	43, M	Hepatitis	70		12				124		105		85		70		372
C.P.	43, M	Hepatitis	21		16				112		82		56		30		164
F.W.	39, M	Cirrhosis	36		18				151		117		93		59		233
F.W.	39, M	Cirrhosis	27		19				129		107		68		41		181
M.W.	29, M	Metast. Ca.			17				81		46		41		37		314
F.Mc.	54, M	Cirrhosis	22	53	14	8	141	19	101	38	78	41	49	35	29	35	168
W.Mc.	59, M	Cirrhosis	36	63	19	13	155	23	94	33	78	52			30	34	180
V.B.	43, M	Cirrhosis	32	56	4	11	102	18	71	19	59	28	31	29	22	40	170
V.B.	43, M	Cirrhosis	22		5	14	108	31	77	37	55	44	33	54	27	42	198
W.B.	60, M	Cirrhosis	39	79	16	2	160	28	108	35	65	33	44	31	31	28	177
K.H.*	51, M	Cirrhosis & p.c. shunt	28	101	9	0	79	3	77	6	70	8	53	8	35	3	264
	MEAN				14	10	133	24	103	32	78	40	54	37	36	36	210
	S.E.M.±				1.6	2.1	11.6	2.3	7.6	3.4	7.1	4.1	7.0	5.8	4.6	2.1	21
Liver Disease with Ascites																	
J.M.	55, M	Cirrhosis	7		8				79		65		44		31		92
J.M.	55, M	Cirrhosis	7		10				84		63		42		25		176
C.P.	60, M	Cirrhosis	48	74	11				103		99		68		56		317
C.P.	60, M	Cirrhosis	35		11				113		81		53		41		209
P.J.	60, M	Cirrhosis	32	85	15				127		91		86		60		317
H.S.	60, M	Cirrhosis	18	87	5				66		45		25		7		96
E.T.	62, M	Cirrhosis	18		12				110		82		53		42		217
D.Q.	54, M	Cirrhosis	9		8				87		63		42		27		183
G.F.	58, M	Cirrhosis	28	76	17	11	140	20	115	22	89	22			41	14	205
M.G.	42, F	Cirrhosis	26	70	13	3	122	9	113	10			65	10	45	9	226
P.S.	38, M	Cirrhosis	26	50							54	18			39	13	512
M.L.	60, M	Cirrhosis	40	79	9	7	131	8	72	19	72	37	58	27	40	27	345
M.L.	60, M	Cirrhosis	40		13	6	130	8	86	13	65	14	59	16	38	17	282
L.B.†	35, M	Cirrhosis & hepatic coma		35	4	8	80	8	73	8	58	8	47	8	39	10	347
	MEAN				11	7	131	11	96	16	72	23	54	18	38	16	244
	S.E.M.±				1.0	1.1	3.7	2.9	5.6	2.8	4.6	4.8	4.9	5.0	3.8	3.0	31
	COMBINED MEAN				12		132		99		75		54		37		229
	S.E.M.±				0.3		6.5		4.6		4.1		4.0		2.9		19

* Not included in figure or calculation of mean—portacaval shunt.

† Not included in figure or calculation of mean—hepatic coma.

mean, S.E.M.) minutes (Fig. 1). The slope of the line depicting the disappearance of the free 17-OHCS from the plasma of normal subjects was -0.162 and the half-life was 112 ± 5 minutes (7). There were no significant differences between the plasma levels of free 17-OHCS in cases of liver disease with ascites and those in cases of liver disease without ascites. As previously reported (1), in both normal subjects and those with liver disease, the rate of removal of free 17-OHCS from the plasma was proportional to the concentration at any given time, but the free 17-OHCS disappeared much more slowly in the liver-disease group. There was good corre-

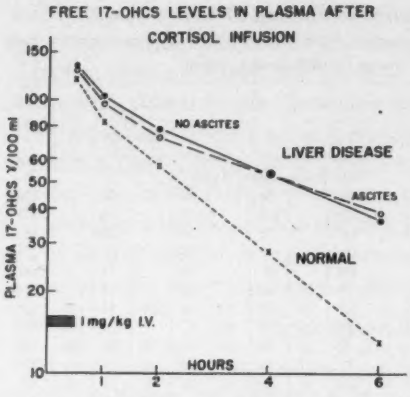

FIG. 1. Mean levels of free 17-OHCS in the plasma after intravenous infusion of cortisol. The half-life of the administered cortisol in normal subjects was 112 ± 5 minutes, and in patients with liver disease it was 229 ± 19 minutes.

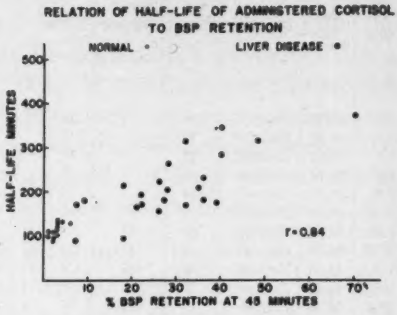

FIG. 2. Relationship of half-life of administered cortisol to bromsulphalein retention. The rate of removal of administered cortisol from the plasma is related to the degree of impairment of liver function. $r = 0.84$.

lation ($r = 0.84$) between the severity of the liver disease as measured by the BSP retention at forty-five minutes and the half-time of 17-OHCS removal from the plasma (Fig. 2).

In comparison with the concentrations in normal subjects, the mean concentrations of conjugated 17-OHCS after the infusion of cortisol in cases of liver disease without ascites rose to somewhat lower levels and then declined more slowly (Fig. 3). The difference between the peak levels at two hours was statistically significant ($P < .05$). In the subjects with liver disease and ascites, the mean 8 a.m. control level of conjugated 17-OHCS in

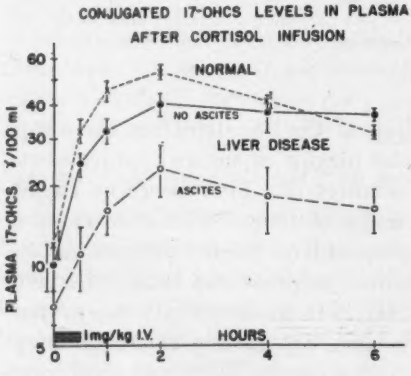

FIG. 3. Mean levels of conjugated 17-OHCS in the plasma after intravenous infusion of cortisol. The levels between brackets include ± 1 standard error of the mean. The difference in plasma levels between normal subjects and those having liver disease with ascites is highly significant, whereas the difference in levels between normal subjects and those having liver disease without ascites is barely significant ($P = 0.05$ at two hours).

the plasma with the S.E.M. was $7 \pm 1.1\gamma$ per 100 ml. as compared with a level of $12 \pm 1.6\gamma$ per 100 ml. in the normal subjects. In these patients the levels of conjugated 17-OHCS in the plasma after the infusion of cortisol were strikingly lower than those in normal subjects and the differences were highly significant statistically (Fig. 3).

In Patient K.H. (Table 1), who had cirrhosis and a portacaval shunt, there was no detectable amount of conjugated 17-OHCS in the plasma prior to the infusion of cortisol, and the maximum level achieved after the infusion was only 8γ per 100 ml.

In Patient L.B. (Table 1), who was studied during an episode of hepatic coma, there was hardly any rise in the level of conjugated 17-OHCS in the plasma during the six-hour period of observation following the infusion of cortisol.

Free and conjugated 17-OHCS in plasma after infusion of tetrahydrocortisone (Tetra E), tetrahydrocortisol (Tetra F) and dihydrocortisone (Di E)

The mean values are plotted in Figure 4. The corresponding mean values in a series of normal subjects (7) are plotted for comparison.

Tetra E. After the infusion of Tetra E, there was a more rapid disappearance of free 17-OHCS from the plasma of the normal subjects and of the patients with cirrhosis than from the plasma of the patients with cirrhosis and ascites. In all three groups the levels of free 17-OHCS declined exponentially for one to two hours at a rate which was much more rapid than the rate after the infusion of cortisol. After the initial phase, the concentration of 17-OHCS declined more slowly.

The conjugated 17-OHCS were at a peak level in the first samples drawn after the completion of the infusion in the normal subjects and in the subjects with cirrhosis of the liver without ascites. The concentrations then exhibited a logarithmic decay. In the patients with cirrhosis and ascites, the peak levels of conjugated 17-OHCS were not reached until fifteen to thirty minutes after the completion of the infusion. The peak level in the subjects with ascites was lower than that in the other two groups. After the initial period, the rate of removal of conjugated 17-OHCS from the plasma of the patients with ascites was about the same as that in the other two groups of subjects.

Tetra F. The disappearance of free 17-OHCS from the plasma after the infusion of Tetra F followed a pattern similar to that after the infusion of Tetra E, but the rate of disappearance was not as rapid (Fig. 4).

The levels of conjugated 17-OHCS after the administration of Tetra F rose to a peak at about thirty minutes after the end of the infusion. After this point the levels declined rapidly for one hour, and then more slowly

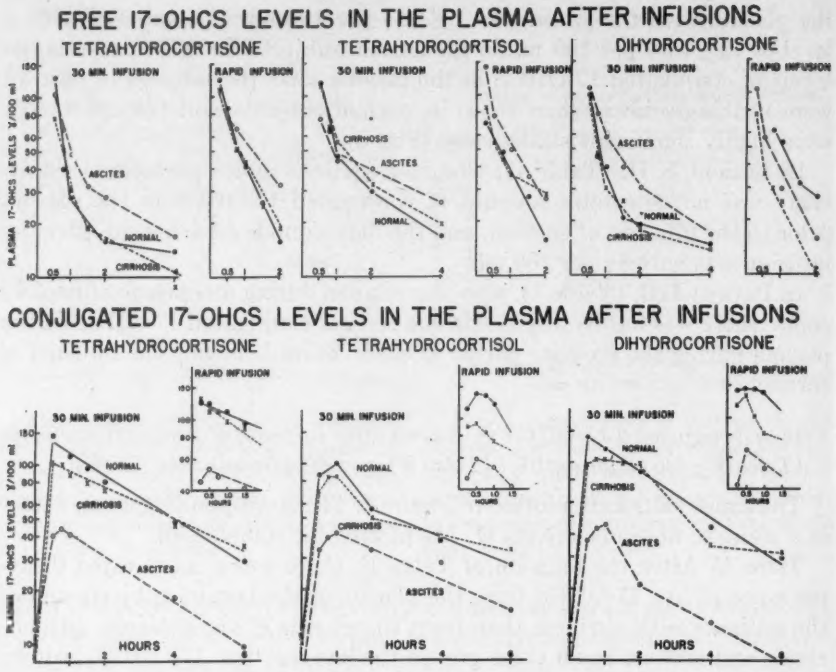

FIG. 4. Mean levels of free and conjugated 17-OHCS in the plasma after 30-minute and rapid infusions of the cortisol reduction products, Tetra E, Tetra F and Di E.

in an exponential fashion. The levels of conjugated 17-OHCS in the patients with cirrhosis and ascites did not exhibit the initial phase of rapid disappearance. Again, the levels of conjugated 17-OHCS in the plasma of the patients with cirrhosis and ascites were considerably lower than the levels in the other subjects studied.

Di E. The removal of free 17-OHCS from the plasma after the infusion of Di E followed a pattern similar to that following infusion of Tetra E.

The levels of conjugated 17-OHCS in the plasma of the normal subjects were at about peak value in the first specimen drawn after the completion of the infusion, and then declined logarithmically after the 30-minute infusion. In the patients with liver disease, the level of conjugated 17-OHCS in the plasma from the first blood sample drawn after the completion of the infusion was not as high as the levels in specimens drawn about thirty minutes later. The levels in the plasma of the patients with ascites were consistently lower than those in the plasma of the other subjects.

Conjugated 17-OHCS in ascitic fluid

The levels of conjugated 17-OHCS in the ascitic fluid of Patient A.S.,

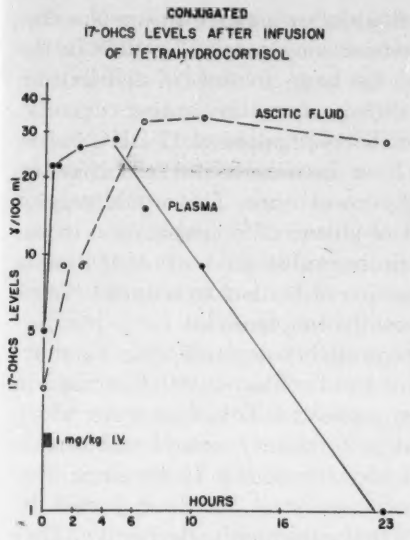

FIG. 5. Levels of conjugated 17-OHCS in the plasma and ascitic fluid of Patient A.S. after the intravenous infusion of Tetra F. Note the rapid removal from the plasma, the time-lag for diffusion into ascitic fluid, and the slow removal from the ascitic fluid.

who received an infusion of Tetra F, are shown in Figure 5. The concentration of 17-OHCS rose to a maximum in about six hours and then changed very little during the next seventeen hours. The levels in the plasma were maximal at four hours after the infusion and then declined rapidly at a rate proportional to the concentration. The maximum level in this patient was much lower than the maximum level achieved in subjects without ascites after a similar infusion (Fig. 4).

DISCUSSION

The results of the present study indicate that there is some impairment of formation of conjugated 17-OHCS following the infusion of cortisol in subjects with liver disease. Other workers (5, 6) have reported similar observations after the oral administration of cortisone and the intravenous administration of adrenocorticotropin (ACTH) to patients with cirrhosis of the liver. However, it has not been emphasized that the magnitude of the apparent defect is markedly affected by the presence of fluid retention. After infusion of cortisol in cases of liver disease without ascites, the rise in the levels of conjugated 17-OHCS was slightly but significantly ($P < .05$) less than that in normal subjects. In patients with ascites, the levels of conjugated 17-OHCS in the plasma, both before and after the infusion of cortisol, were strikingly less than those in normal subjects. In this laboratory, appreciable levels of conjugated 17-OHCS have been found consistently in samples of all extracellular fluids except spinal fluid. In 1 patient in the present study, the accumulation of large amounts of conjugated 17-

OHCS was demonstrated in the ascitic fluid following an infusion of a corticosteroid. It is likely that the low levels of conjugated 17-OHCS in the plasma of subjects with ascites reflected the large volumes of distribution of conjugated 17-OHCS rather than a difference in conjugating capacity.

The apparent impairment of glucuronide conjugation of 17-OHCS after the infusion of cortisol in patients with liver disease was not seen after the infusion of its metabolic product, tetrahydrocortisone. This would suggest that there is no detectable impairment of glucuronide conjugation in patients with liver disease, provided the proper substrate for conjugation is supplied. The delay is in the transformation of cortisol to reduced 17-hydroxycorticosteroids, which are then readily conjugated.

The reduction of circulating cortisol probably depends upon an enzymatic reaction within the liver. Tomkins and Isselbacher (10) described in rat liver a specific triphosphopyridine nucleotide-linked enzyme which catalyzes the reduction of the Δ^4 bond of cortisone, cortisol and certain other steroids to the corresponding dihydro compound. In the same liver fraction, there was also another less specific enzyme, 3-hydroxysteroid dehydrogenase, which reduced the dihydro to the tetrahydro derivative. They postulated that the first reaction was rate controlling and that the reduction of dihydrocortisone to tetrahydrocortisone was more rapid than the over-all reaction, inasmuch as dihydrocortisone did not accumulate in the reaction vessel. Additional evidence that dihydrocortisone is further reduced prior to glucuronide conjugation is suggested by failure to identify it in the conjugated fraction in human plasma (6).

From the limited data reported here, there is also a suggestion that Di E and Tetra F are further transformed in man prior to conjugation with glucuronide. The levels of conjugated 17-OHCS after the infusion of these steroids in normal subjects as well as in those with liver disease were not maximal in the plasma until some time after the completion of the infusion. In contrast, the levels following administration of Tetra E were at their peak in the plasma of the first blood specimen drawn after completion of the infusion. It is reasonable to attribute this delay to the time required for additional reactions prior to conjugation.

Isselbacher and Axelrod (11) have demonstrated the conversion of Tetra E or Tetra F to the corresponding glucronide conjugate in an *in vitro* system containing cell-free preparations of liver in the presence of uridine diphosphate glucuronide. This reaction was not reversible. Cortisone was not metabolized in this system. This would suggest that reduction of the 3-ketone to the 3-hydroxyl is necessary for conjugation, and that the probable site of coupling on the steroid molecule is at the 3-hydroxyl position as in the case of pregnanediol 3-β-*d*-glucuronide (12).

Since Tetra F is a suitable substrate for conjugation (11) and Tetra F

glucuronide is present in normal human plasma (6), no explanation for the delayed peak in the formation of conjugated 17-OHCS after infusion of Tetra F is evident. It may be pertinent to point out, however, that although cortis*ol* is the principal free 17-OHCS in plasma (13), tetrahydrocortis*one* is the principal 17-OHCS in urine (2). Perhaps the kidney may be involved in the oxidation of the 11β-hydroxyl group to an 11-ketone after conjugation.

It is of considerable interest that Diczfalusy, Birke and Plantin (14) found that the conjugation of estrogens in patients with cirrhosis of the liver was analogous to the conjugation reported here. When estradiol was administered to these patients, low levels of conjugated estrogen were found in the urine and "the conversion of free estradiol to estriol appeared to be very low."

It would appear that the conjugation mechanism is a very fundamental one and is preserved even in the presence of severe liver damage. The levels of conjugated 17-OHCS after the infusion of cortisol were extremely low in Patient L.B. (Table 1), who was in a state of "hepatic coma." On the other hand, the levels of conjugated 17-OHCS in a second case of "hepatic coma" after an infusion of Tetra E were in the same range as in normal subjects. In Patient K.H. (Table 1), who had a functioning portacaval shunt resulting in episodic attacks of dietary portal-systemic encephalopathy (15), similar impairment was noted after infusion of cortisol in the absence of ascites. However, normal conjugation was observed after infusion of Tetra E.

As in earlier studies (1), it was apparent that there was a decreased rate of removal of free 17-OHCS from the plasma of patients with liver disease and that there was good correlation between the rate of removal and the functional capacity of the liver, as measured by the bromsulphalein retention test. In contrast to the rate of disappearance of cortisol, the rate of disappearance of cortisone, as reported by Peterson and associates (16), was not strikingly different from normal in a single patient with cirrhosis of the liver.

Since hepatic blood flow may be reduced in patients with cirrhosis of the liver (17), the delayed removal of free 17-OHCS after administration of cortisol may be due in part to decreased blood supply to the liver. Studies in our laboratory (18) have demonstrated an impairment of removal of free 17-OHCS and of formation of conjugated 17-OHCS after infusion of cortisol in dogs with surgical devascularization of the liver and without demonstrable hepatic histologic changes. The levels of conjugated 17-OHCS after administration of Tetra E have not been studied in these animals.

In the present study the levels of "Porter-Silber chromogens" (19) in the

plasma after infusions of cortisol and certain of its reduction products were measured in order to study conjugation of 17-OHCS in patients with liver disease. From the patterns of the levels of conjugated 17-OHCS in the plasma after the infusions, the metabolic pathway for removal of cortisol is suggested. However, it should be emphasized that the methods employed in this investigation measure only the 17,21-dihydroxy,20-ketosteroids, which include cortisol, cortisone, Reichstein's substance S and their hydrogenated derivatives. In the normal subject, cortisol is the chief constituent of the free 17-OHCS in the plasma (13), but the Porter-Silber chromogens will account for only 20–30 per cent of the metabolic products of cortisol in the urine (16). Moreover, in patients with liver disease, it is possible that cortisol metabolism may be partially diverted to abnormal or normally minor pathways (20). Qualitative analysis of cortisol metabolites would provide useful information concerning these variables, but it was not within the scope of the present study. It is well to remember that, although the liver is the principal site of metabolism of circulating 17-OHCS, it is probable that other tissues participate (21). This participation may assume greater importance when normal mechanisms are blocked in the presence of liver disease.

SUMMARY

1. After infusion of cortisol, there was a decreased rate of removal of free 17-hydroxycorticosteroids (17-OHCS) from the plasma of patients with liver disease. The half-life of the administered cortisol was 229 ± 19 minutes as compared with a half-life of 112 ± 5 minutes in a group of normal subjects. The rate of removal was correlated with the severity of hepatic impairment as estimated by bromsulphalein retention.

2. The levels of conjugated 17-OHCS in the plasma after an infusion of cortisol were lower than normal in patients with liver disease and markedly lower than normal in patients with liver disease and ascites. The low levels in subjects with ascites were attributable to the large volume of distribution of conjugated 17-OHCS.

3. The apparent impairment of 17-OHCS conjugation after the infusion of cortisol in patients with liver disease was not observed after the infusion of tetrahydrocortisone. This was interpreted as evidence that, in disease of the liver, there is impairment of reduction of cortisol to its hydrogenated metabolites which are the substrates for conjugation.

4. In the presence of suitable substrate, conjugation proceeds normally in patients with liver disease.

5. After infusion of the metabolites of cortisol (Tetra E, Di E, and Tetra F) in patients with liver disease, the rates of removal of free 17-OHCS from the plasma and of appearance of conjugated 17-OHCS in the plasma were strikingly faster than after the infusion of cortisol itself.

6. Minor delays in the appearance of peak levels of conjugated 17-OHCS in the plasma of patients with liver disease were observed after infusion of Di E or Tetra F, but were not seen after infusion of Tetra E.

Acknowledgments

The authors wish to acknowledge the contribution of the Sharp and Dohme Division of Merck and Co. for supplies of corticosteroids; the assistance of Mrs. Janet Nicoll and her metabolic ward staff; the preparation of charts and photographs by Mr. Keith Johnson; the technical assistance of Mrs. Barbara Samuels; and the helpful advice of Dr. L. T. Samuels and Dr. M. M. Wintrobe.

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MAGNESIUM STUDIES IN RELATION TO HYPERPARATHYROIDISM

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IN THE clinical study of hyperparathyroidism there have been few contributions concerning the metabolism of magnesium. The studies of Bulger and Gausmann (1), Bassett and Alstine (2, 3), and Tibbetts and Aub (4) are confirmed and extended here in relation to a patient requiring two operations for the removal of a hyperfunctioning parathyroid tumor. In view of the chemical similarity of magnesium and calcium it might be supposed that these elements are both affected in hyperparathyroidism. In order to obtain further information on magnesium metabolism in this disorder a balance study was conducted in a case of hyperparathyroidism, prior to and following extirpation of an active parathyroid tumor. The results of this study, as well as pertinent background for their interpretation, are considered here.

EXPERIMENTAL APPROACH

Application of balance technique to magnesium studies

Previous balance studies on healthy subjects (4–9) revealed three main difficulties:

1) Magnesium intakes are more than adequate, and this obscures minor physiologic alterations in the metabolism of magnesium. The adult requirement for magnesium has not been established or confirmed (10–14). In a recent review (15) it was said to be less than 10 mg. or 0.83 mEq. per day during growth. Presumably the requirement is less in adult life, and is far exceeded in magnesium balance studies.

2) The metabolism of magnesium is altered not only by the intake of magnesium, but by the intake of calories, nitrogen, phosphorus and calcium.

Received March 28, 1957.

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3) The analytical techniques are difficult and subject to errors when determining magnesium in the presence of other ions.

Interdependence of nitrogen and magnesium balances

The importance of considering the nitrogen balance in the interpretation of the magnesium balance is demonstrated by the data on Benedict's fasting patient (16). During the final ten days of the 31-day fast the magnesium-nitrogen ratio was 0.55 (mEq./Gm.). For comparison, the potassium-nitrogen ratio during the same period was 2.2 (mEq./Gm.). These ratios are significantly lower than the magnesium-nitrogen ratio of 0.63 and the potassium-nitrogen ratio of 3.5 found in skeletal muscle (17, 18). The catabolism of severe diabetic acidosis was studied by Butler (19), and during 4.4 days of advancing acidosis magnesium and nitrogen were excreted in the ratio of 0.88 (mEq./Gm.) and potassium and nitrogen in the ratio of 6.5 (mEq./Gm.). These values indicate the distortion such ratios may undergo in conditions of severe metabolic disturbance. Considering the well-established compensatory mechanisms available to the body in combating a metabolic acidosis, the greater relative loss of magnesium and potassium to that of nitrogen was to be expected.

In contrast, the accretion of magnesium in relation to nitrogen and potassium may be determined from Swanson's study (20) of growth in infancy. The magnesium-nitrogen ratio was 1.4 (mEq./Gm.) and the potassium-nitrogen ratio was 5.3 (mEq./Gm.) between the third and sixth months of age. From these ratios we infer either that during infancy the protoplasm that is formed is significantly richer in these minerals than is adult skeletal muscle, or that unmeasured losses of minerals (possibly in perspiration) resulted in a spurious increase in the reported infant mineral-nitrogen ratios. The magnesium-nitrogen ratio of 1.4 was, in part, a consequence of the additional amounts of magnesium required for skeletal growth.

Magnesium content of bone

The calcium-magnesium ratios in bone on a weight basis have been variously expressed as 38 in mature dogs (21), as 36 to 59 in rats as they mature from 1 month to 5 months in age (22), as 72 in rats (10), and as 33 to 100 in human bone (14). (The percentage content of magnesium in bone ash stated by Duckworth and Warnock (14) as ranging between 0.4 and 1.2 per cent has been converted to a calcium-magnesium ratio, assuming bone ash contains 40 per cent calcium by weight.) These findings do not agree, and we conclude that the magnesium content of bone ash is in fact a variable. This is most likely a consequence of the inevitable inclusion in whole-bone analysis of the magnesium that is extracellular and intimately related to the supporting crystalline structure, and the magnesium that is

intracellular. These two sources of magnesium vary widely in their relative proportions in whole bone. Support for this interpretation of the fluctuations in magnesium content is seen in: a) the parallel relationship between magnesium and the water content of bone, suggesting an associated intracellular accumulation (22), and b) the relative increase in magnesium in bone derived from calcium-deficient animals in which there is a considerable increase in the cellularity due to the presence of unmineralized osteoid tissue (12). Contrariwise, hydrolysis of bone with trypsin has been reported not to decrease the magnesium content, thus implying no significant association between the proteins of bone and magnesium (23). Work reported by Duckworth *et al.* (24–26) was conducted in the growing rat, and bizarre deficiencies and re-allocations of the supplies of magnesium were produced. How far the conclusions from these weanling rats may be applied to humans is open to conjecture. At present the possibility of a specific mobilization of magnesium from bone, apart from that of calcium and phosphorus, appears unsettled.

In interpreting the balance study, we have accepted the following ratios (17) as representative of the concentration of nitrogen in grams, magnesium in milliequivalents, and phosphorus in grams, in normal skeletal muscle—1.0:0.63:0.065. We have adopted the following ratio (27) as representative of phosphorus in grams and calcium in grams in normal bone—1.0:2.2.

METHOD OF STUDY

The balance technique employed and the analytical methods for nitrogen, calcium, and phosphorus were similar to those reported previously from this hospital (28). The amounts of magnesium ingested and excreted in the urine and feces were determined on acid extracts of ashed specimens by a colorimetric method coupling the magnesium ion with titan yellow dye, as reported by Garner (29). The limitations of this procedure (30, 31) must be considered when applying the titan yellow method to the determination of magnesium in the presence of calcium, phosphorus, and other interfering substances.

The foregoing balance technique was applied only to metabolic periods I through V prior to the removal of a hyperfunctioning parathyroid tumor and to metabolic periods VI and VII following its excision, for a detailed study of the relationships of nitrogen, magnesium, phosphorus and calcium. In Figure 1 are shown complementary data on only the magnesium balance and caloric intake over a more extended interval; these were obtained by calculating the magnesium and caloric content of the food from standard food tables (32–34). A check comparison of the magnesium content derived from food tables with that determined by analysis indicated that the analytical values for the diet were approximately 18 per cent lower than anticipated by calculations based on the tables. Therefore, when the balance study involves magnesium *alone*, the recorded intake of magnesium may be consistently higher than the actual intake.

BALANCE DATA

The data are presented in 3 tables and in 2 figures derived from these tables. Table 1 is concerned with the serum values for magnesium, calcium,

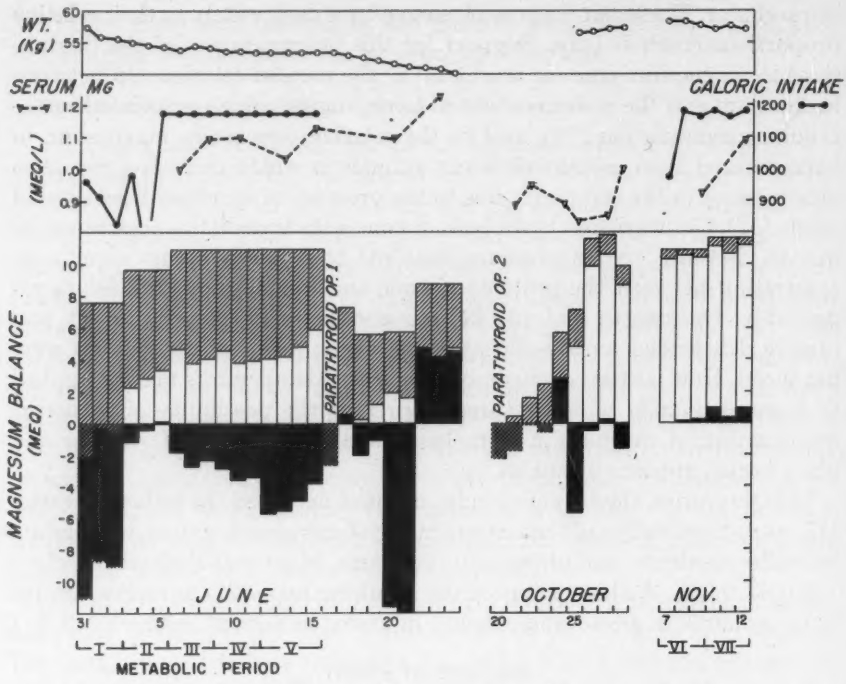

FIG. 1. Magnesium balance and caloric intake before and after 2 parathyroid operations.

The charting convention employed is the same as that shown in the lower right-hand corner of Figure 2. The intake for any component is measured from the baseline upwards, and the output is measured from the top of the column downwards. When the total output falls above the baseline, a black area represents a positive balance, and when the total output falls below the baseline, a black area represents a negative balance (35). The cross-hatched areas represent the urinary losses, and the losses by stool are designated by the space below the urinary losses. If there are losses by stool, these are represented by the area below the urinary losses to the top of the black column when a positive balance exists, and to the bottom of the black column when a negative balance exists. Thus the stool area may be clear, black, or a summation of clear and black areas

and related components. It reveals the consistently elevated calcium levels and the depressed phosphorus levels prior to the resection of the hyperfunctioning parathyroid tumor, and the reversal of these values following the second operation. The abnormally low concentration of serum magnesium (normal = 1.7 mEq./L; S.E. = 0.04) prior to the removal of the hyperfunctioning parathyroid tumor became still lower after the second operation. These are significant departures from normal values, and significant changes as well. Table 2 is concerned with the values for the daily

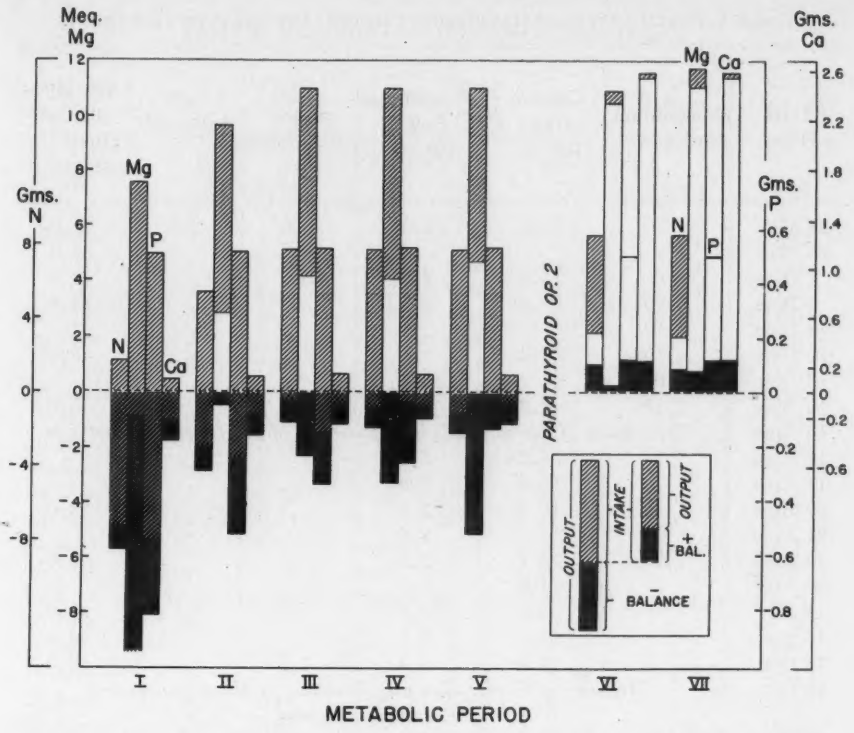

FIG. 2. Nitrogen, phosphorus, calcium and magnesium balance data, in metabolic periods.

The charting convention employed here is the same as that explained in the legend of Figure 1, and is illustrated in the lower right-hand corner.

magnesium balance and caloric intake during the seven metabolic periods, and also when the magnesium balance was followed in the two immediate postoperative periods. The overall trends of these data, together with the weight of the patient, the serum magnesium level, and the caloric intake are shown in Figure 1. At the bottom of this figure are defined the seven metabolic periods investigated in greater detail, for related balances of nitrogen, phosphorus, calcium and magnesium, which are presented in Table 3. In this table are listed the intakes for three-day or four-day periods, the pooled urinary and fecal excretions, and the balances, in terms of the daily values based on an average derived from the data covering a particular metabolic period. In Figure 2 these data are charted with the scales adjusted in accord with a method of plotting metabolic data formulated by Reifenstein *et al.* (28). The nitrogen, magnesium and

TABLE 1. SERUM LEVELS OF MAGNESIUM, CALCIUM, AND RELATED COMPONENTS

Date (1955)	Magnesium (mEq./L.)	Calcium (mg./ 100 ml.)	Phosphorus (mg./ 100 ml.)	Total protein (Gm./100 ml.)	A/G ratio	Alk. phosphatase (Bod. U./ 100 ml.)
24 May		14.5	2.0	6.6	2.6	71.0
26 May						51.0
1 June		15.8	2.6			48.0
6 June	1.00	18.4	2.1			48.0
8 June	1.10					
10 June	1.10	8.4				45.0
13 June	1.03					
15 June	1.13	16.2	2.1			45.0
16 June	*Exploration of Parathyroids with Resection of 3½ Hyperplastic Glands*					
17 June		14.2	1.6			
18 June		15.6	2.0			
20 June	1.10	15.6	2.2			33.0
21 June		14.2	1.6			
23 June	1.23	15.1	2.5			35.0
30 June		11.9	1.7			
12 July		13.4	1.8			41.0
18 Sept.		14.8	2.2			53.0
18 Oct.		13.6	2.8	7.1		51.0
20 Oct.	*Mediastinal Exploration with Resection of Hyperfunctioning Parathyroid Tumor*					
21 Oct.	0.89	9.8	1.0			
22 Oct.	0.95	8.6	1.7			
23 Oct.		7.8	1.3			
24 Oct.	0.89	7.8	1.6			35.0
25 Oct.	0.85			7.0		
27 Oct.		7.4	1.7			42.0
29 Oct.	1.00					
1 Nov.	1.03	8.3	1.6			39.0
7 Nov.		7.3	2.3			42.0
9 Nov.	0.92					
10 Nov.		6.8	2.0			32.0
13 Nov.	1.09					
16 Nov.		7.3	3.0			25.0
28 Nov.		6.8	3.2			5.0
21 Dec.		6.5	4.1			5.7

phosphorus scales are adjusted so that equal linear distances on these scales represent quantities of the components in the proportion as they exist in skeletal muscle (17), using the ratios 1.0:0.63:0.065. The calcium scale is adjusted in relation to the phosphorus scale so that equal linear distances on the phosphorus and calcium scales represent proportions of these ele-

TABLE 2. MAGNESIUM BALANCE AND CALORIC INTAKE

Date (1955)	Day	Urine	Stool	Total output	Intake	Balance	Calories
			Metabolic Periods I through V				
31 May	1	9.61	21.3	30.9	7.57	−23.3	963
1 June	2	7.84	21.3	29.1	7.57	−21.5	915
2 June	3	8.05	21.3	29.3	7.57	−21.7	827
3 June	4	7.44	3.33	10.8	9.68	− 1.1	984
4 June	5	6.75	3.33	10.1	9.68	− 0.4	112
5 June	6	6.27	3.33	9.6	9.68	+ 0.1	1181
6 June	7	6.34	6.45	12.8	11.0	− 1.8	1181
7 June	8	7.20	6.45	13.7	11.0	− 2.7	1181
8 June	9	6.85	6.45	13.3	11.0	− 2.3	1181
9 June	10	6.41	7.40	13.8	11.0	− 2.8	1181
10 June	11	7.19	7.40	14.6	11.0	− 3.6	1181
11 June	12	6.95	7.40	14.3	11.0	− 3.3	1181
12 June	13	6.93	9.69	16.6	11.0	− 5.6	1181
13 June	14	6.83	9.69	16.5	11.0	− 5.5	1181
14 June	15	6.23	9.69	15.9	11.0	− 4.9	1181
15 June	16	5.14	9.69	14.8	11.0	− 3.8	1181
16 June	*Exploration of Parathyroids with Resection of $3\frac{2}{3}$ Hyperplastic Glands*						
16 June	0	2.58	0	2.58	0	− 2.6	0
17 June	1	6.70	0	6.70	7.25	+ 0.6	873
18 June	2	5.36	2.22	7.58	5.60	− 2.0	425
19 June	3	4.44	2.23	6.67	5.60	− 1.1	686
20 June	4	3.84	13.5	17.34	5.70	−11.6	443
21 June	5	4.06	13.5	17.56	5.70	−11.9	638
22 June	6	4.12	0	4.12	8.82	+ 4.7	691
23 June	7	4.62	0	4.62	8.82	+ 4.2	792
24 June	8	4.24	0.17	4.41	8.83	+ 4.4	849
20 Oct.	*Mediastinal Exploration with Resection of Hyperfunctioning Parathyroid Tumor*						
20 Oct.	0	2.29	0	2.29	0	− 2.3	200
21 Oct.	1	2.12	0	2.12	0.40	− 1.7	391
22 Oct.	2	1.67	0	1.67	1.61	− 0.1	967
23 Oct.	3	2.99	0	2.99	2.40	− 0.6	645
24 Oct.	4	2.88	0	2.88	5.70	+ 2.8	850
25 Oct.	5	2.38	10.4	12.8	7.08	− 5.7	851
26 Oct.	6	1.66	10.4	12.1	11.6	− 0.5	1145
27 Oct.	7	1.20	10.4	11.6	11.8	+ 0.2	1181
28 Oct.	8	1.15	10.4	11.6	9.93	− 1.7	1085
			Metabolic Periods VI and VII				
7 Nov.	1	0.59	10.3	10.9	10.9	0	975
8 Nov.	2	0.41	10.3	10.7	10.9	+ 0.2	1181
9 Nov.	3	0.44	10.3	10.7	10.9	+ 0.2	1166
10 Nov.	4	0.51	10.3	10.8	11.7	+ 0.9	1181
11 Nov.	5	1.03	10.3	11.3	11.7	+ 0.4	1165
12 Nov.	6	0.47	10.3	10.8	11.7	+ 0.9	1181

TABLE 3. DAILY NITROGEN AND MINERAL BALANCES

Metabolic period		Balance study, May 31 through June 15											
No.	Duration (days)	N (Gm.)	Mg (mEq.)	P (Gm.)	Ca (Gm.)	N (Gm.)	Mg (mEq.)	P (Gm.)	Ca (Gm.)	N (Gm.)	Mg (mEq.)	P (Gm.)	Ca (Gm.)
		Urine				*Feces*				*Total*			
I	3	8.93	8.5	1.05	0.311	1.39	21.3	0.279	0.188	10.3	29.8	1.33	0.499
II	3	8.30	6.8	0.749	0.290	1.39	3.3	0.279	0.188	9.70	10.1	1.03	0.478
III	3	8.14	6.8	0.676	0.237	1.23	6.5	0.183	0.160	9.37	13.3	0.859	0.397
IV	3	8.54	6.9	0.567	0.221	1.08	7.4	0.213	0.123	9.62	14.3	0.780	0.344
V	4	8.80	6.3	0.525	0.195	1.06	9.7	0.139	0.185	9.86	16.0	0.664	0.380
		Intake				*Balance*				*% Total output in stool*			
										Mg	Ca		
I	3	1.78	7.6	0.501	0.101	−8.5	−22.2	−0.83	−0.40	71	38		
II	3	5.42	9.78	0.510	0.122	−4.3	− 0.4	−0.52	−0.36	33	39		
III	3	7.68	11.0	0.526	0.132	−1.7	− 2.3	−0.33	−0.27	49	40		
IV	3	7.68	11.0	0.526	0.132	−1.9	− 3.3	−0.25	−0.21	52	36		
V	4	7.68	11.0	0.526	0.132	−2.2	− 5.0	−0.14	−0.25	61	49		
		Balance study, November 7 through November 12											
		Urine				*Feces*				*Total*			
VI	3	5.28	0.48	0.0	0.015					7.05	10.8	0.38	2.33
VII	3	5.47	0.67	0.0	0.014					7.24	11.0	0.38	2.32
VI and VII	6					1.77	10.3	0.38	2.31				
		Intake				*Balance*				*% Total output in stool*			
										Mg	Ca		
VI	3	8.52	10.9	0.50	2.58	+1.47	+0.1	+0.12	+0.25				
VII	3	8.52	11.7	0.50	2.58	+1.3	+0.7	+0.12	+0.26				
VI and VII	6									95	99		

ments as they exist (27) in normal bone *i.e.*, 1.0:2.2. There is no meaningful relation between the calcium and nitrogen or magnesium scales. The equivalence of scales is often an arbitrary matter, and the plot chosen here is deliberately designed to facilitate the interpretation of the data on the assumption that nitrogen, magnesium and phosphorus are mobilized from, and deposited together in skeletal muscle or in a tissue of essentially the same composition. Likewise the calcium and phosphorus scales are mutually adjusted on the assumption that the dissolution or the formation of bone will yield or will require fixed proportions of these elements. The magnesium content of bone is ignored on the supposition that it is not part of an active metabolic pool of magnesium available as a significant buffer against the fluctuating demands for magnesium, in the sense that bone calcium definitely appears to be in relation to body calcium. The validity of this assumption will be tested most readily by tracer isotope techniques. In these studies the amount of magnesium that would be mobilized with calcium from bone, if one assumes a uniform distribution of

magnesium and calcium in the skeleton, is far less than the experimental error of the balance technique employed.

CASE REPORT

This 37-year-old white man (MGH Parathyroid Case No. 172) was first admitted to the hospital in 1953, at which time he was treated for a cyst of the mandible seen on a dental film. At the time of this admission nothing remarkable was noted in the patient's history or on physical examination. Serum chemical determinations were not obtained, and the results of urinalysis were not remarkable. Under novocaine anesthesia, the cyst was excised together with the overlying bone to provide a diagnosis. Grossly the tumor had a gritty appearance consistent with fibrous dysplasia. The area was curetted thoroughly, and all gross tumor was removed. At the operation a frozen section was obtained; the histologic picture was reported as being consistent with benign giant-cell tumor. The cavity was treated with phenol and alcohol prior to primary closure of the incision. The incision healed uneventfully, and the final pathologic report was benign giant-cell tumor, although the reservation was made that a brown tumor of hyperparathyroidism could not be excluded. The possibility of a diagnosis of hyperparathyroidism was not pursued.

The patient continued to have some aching in his jaw, and noted that his teeth were loose. He was found to have chronic pyorrhea. Two years later he experienced some dysuria, which was diagnosed as a mild inflammation of the prostate gland. He had no renal stones, urinary gravel or hematuria, and he denied any weakness, mental confusion, vomiting or polyuria, although drinking approximately seven to eight glasses of water a day. X-ray films were again taken because of the continued aching in his jaw, and these now revealed many additional skeletal abnormalities, including "bone cysts," that were consistent with hyperparathyroidism.

A second hospital admission followed, so that further studies could be made. The patient denied an excessive consumption of milk or dairy products, although approximately four years prior to admission he had been studied intensively because of symptoms which were thought to be consistent with a peptic ulcer. An ulcer had been identified by x-ray examination, although the evidence was not strong, and the patient did not maintain a rigid ulcer routine following this disclosure. Other details in the past history were not remarkable.

Upon physical examination there were no unusual findings, and there was no palpable mass in the neck. Laboratory data: Blood—hemoglobin level 13.8 Gm. per 100 ml.; white blood cells 8,400 per cu. mm., with a normal differential count. Urine—pH 6.0, specific gravity 1.012, albumin +, sugar 0, acetone 0, bile 0; the sediment contained 15 to 20 white cells, rare red cells and occasional casts per high-power field. Most of the serum chemical determinations are listed in Table 1. The serum nonprotein nitrogen level was repeatedly found to be normal or only slightly elevated. Further x-ray studies revealed diffuse demineralization of the calvarium, mandibles, extremities and upper cervical spine, absence of the lamina dura, and a moderate degree of nephrocalcinosis. The basal metabolic rate was −5 per cent.

A balance study was undertaken for a period of sixteen days prior to the surgical exploration of the parathyroid tissue in the neck. At operation on June 16, 1955, all 4 parathyroid glands were identified in the neck and found to be slightly hyperplastic. Three whole glands and two-thirds of the left upper gland were removed, in the expectation that subtotal resection of the cervical parathyroid tissue would alleviate the patient's condition. Following the operation he had an uneventful convalescence, during

which time a magnesium balance study was conducted for eight days. The serum chemical values did not change appreciably, and it was believed that the patient must have additional functioning parathyroid tissue. The histologic diagnosis was hyperplasia, chief-cell type, affecting all 4 parathyroid glands.

Confirmation of the diagnosis by means of the serum chemical determinations shown in Table 1 indicated the necessity of a mediastinal exploration. Therefore, a second operation through a sternum-splitting incision was performed on October 20, 1955. Within the substance of the right upper quadrant of the thymus gland a characteristic parathyroid tumor was discovered, measuring approximately $1 \times 2\frac{1}{2} \times 2\frac{1}{2}$ cm. This was removed along with the adjoining thymus tissue. Following the operation, the serum chemical levels changed as noted in Table 1, indicating a relative deficiency of parathyroid hormone. During the uneventful convalescence, complicated only by symptoms of mild tetany, a second magnesium balance study was conducted for the first eight postoperative days. On discharge from the hopsital the patient received a high-calcium and high-magnesium diet. He was readmitted on the seventeenth postoperative day for the final six-day balance study designated as metabolic periods VI and VII. By then it was thought that the initial physiologic alterations most conspicuously related to such factors as anesthesia, surgical trauma and medication would be of less moment and that the full tide of the physiologic adjustment related to the removal of the hyperfunctioning parathyroid tissue would be apparent. The patient remained in the hospital for six days and then was unable to participate further in these volunteer studies. The histologic diagnosis of the mediastinal tumor was parathyroid adenoma in the thymus gland; the cell type was similar to that in the previous removed hyperplastic parathyroid glands.

INTERPRETATIONS

The study reported here is of interest from three aspects: 1) comparison of the relative balances of nitrogen, magnesium, phosphorus and calcium in a patient with a hyperfunctioning parathyroid tumor, before and after its removal, 2) comparison of the magnesium balances immediately following an exploratory operation and after a similar operation during which a hyperfunctioning parathyroid tumor was removed, and 3) comparison of the findings in this case with those of previous balance studies reported in the literature.

As charted in Figure 2, the balance data of nitrogen, magnesium, phosphorus and calcium before and after removal of the parathyroid adenoma reveal a striking and apparently consistent modification of the way in which these elements were conserved by this patient. During metabolic periods III, IV, V, VI and VII, the nitrogen, magnesium, phosphorus and caloric intakes were almost identical. To avoid symptoms of severe tetany the calcium intake was increased considerably in periods VI and VII. In the first two metabolic periods the caloric intake was intially on the low side, but during the third, fourth and fifth metabolic periods the caloric intake was maintained at a level satisfactory for the sedentary routine of hospital life. The interpretations of the balance as influenced by hyper-

functioning parathyroid tissue are limited to these three periods during which the caloric intake was adequate, constant, and not associated with any meaningful weight change. In these periods the balance for nitrogen was slightly negative and the balances for magnesium, phosphorus and calcium were markedly negative. In periods VI and VII, after the excision of the parathyroid adenoma, during a period of similar caloric intake the balances of nitrogen, magnesium, phosphorus and calcium were positive, in association with a marked diminution in the excretion of magnesium, phosphorus and calcium in the urine. The absence of phosphorus in the urine and the pronounced decrease in urinary calcium following the removal of the hyperfunctioning parathyroid tumor are in accord with previous experience in the study of this disease. Comparisons of the relative balances of nitrogen, magnesium, phosphorus and calcium in a qualitative sense are indicated in Figure 2. If one accepts the scales as a means of testing the hypothesis upon which they were constructed, the negative balance of magnesium in periods III, IV and V appeared to be in excess of that which may be accounted for by the excretion of nitrogen. The accretion of magnesium in periods VI and VII was not matched with an appropriate amount of nitrogen. In the combined metabolic periods III, IV and V, the agreement between the determined phosphorus balance and the one theoretically anticipated on the basis of the calcium and nitrogen excretion was within 1 per cent—partly a fortuitous circumstance. In metabolic periods VI and VII the phosphorus accumulation was only slightly in excess of that expected on the basis of the positive calcium balance. In these periods the calcium balance was less precisely defined because of the large intake.

In summary, there appeared a negative nitrogen balance prior to the removal of the hyperfunctioning parathyroid tumor and a positive balance in the period of observation following its removal. The magnesium, phosphorus and calcium balances were likewise reversed. There was an excessive loss of magnesium in relation to nitrogen in the periods prior to the removal of the tumor. The actual and theoretical losses of phosphorus were in good agreement in the preoperative periods. However, in periods VI and VII the interpretation of the data in terms of the expansion or contraction of the mass of skeletal muscle or bone is not satisfactory. Clearly such an interpretation in the last two periods is only a rough approximation of the actual state of affairs.

The magnesium balance studies immediately following the two operations involving practically identical amounts of tissue trauma, anesthesia, and postoperative medication are shown in Figure 1. The first of the two operations provided an appropriate control observation. No significant influence of such factors as anesthesia, hospitalization, and analgesic drugs

on the magnesium balance was discernible apart from that to be anticipated on the basis of a reduced oral intake and delayed bowel function. The positive balance on the sixth through eighth postoperative days after the first operation is believed to be spurious, due to a retention of the stools. The magnesium balances after the second operation were distinctly different, and a comparison with the balances after the first operation is only slightly impaired by the fact that dietary intake was not as promptly restored. It might be asked whether the difference in magnesium excretion after the second operation could be related to the decreased dietary intake. It is noteworthy in this regard that during the fourth through eighth postoperative days, when the intake was equal to or greater than the intake following the first parathyroid exploration, the urinary excretion of magnesium was reduced. This strongly suggests that the prompt renal conservation of magnesium was not dependent on the initial low intake. After approximately three weeks, in metabolic periods VI and VII a positive magnesium balance was established. The low levels of serum magnesium were unchanged following the first parathyroid operation, but following the second operation there was a definite decrease to unusually low levels in spite of the renal conservation. One may conjecture that this was a manifestation of bone or tissue avidity for magnesium.

In summary, the magnesium balances following two parathyroid gland explorations indicate that the prompt alterations in magnesium excretion were not dependent on such ancillary factors as anesthesia, bed rest and analgesic drugs. The changes noted after removal of the parathyroid tumor were presumably associated with a decreased amount of circulating parathyroid hormone. The renal conservation of magnesium as measured in metabolic periods VI and VII contributed to the positive balance established by the end of the third postoperative week.

These studies may be compared with three previous clinical reports that have come to our attention, describing alterations in magnesium metabolism in relation to hyperparathyroidism. Bulger and Gausmann (1) noted a tendency toward loss of magnesium in a case of clinical hyperparathyroidism (No. 26253), but as they did not report the weight of the patient or the nitrogen balance, the interpretation of the data is not clear. In the recovery phase following the extirpation of a parathyroid tumor these authors noted a positive balance of magnesium, but in the absence of nitrogen data this fact is subject to several interpretations.

A balance study carried out by Bassett and Alstine (3) extended over a 21-day preoperative period and a 27-day postoperative period following the removal of a 1.3-gram parathyroid adenoma from a 20-year-old girl. The serum calcium level dropped from over 12 mg. per 100 ml. to less than 9 mg. per 100 ml., and mild symptoms of tetany were present for a few days

following the operation. Unfortunately, in this detailed study there was no record of the serial weights of the subject, so the meaning of the positive balances is uncertain. The average daily balances in the preoperative and postoperative study periods increased as follows: nitrogen from +0.9 to +1.7 Gm., magnesium +1.2 to +3.4 mEq., phosphorus +0.18 to +0.57 Gm., and calcium +0.17 to +0.88 Gm. Probably this subject was gaining weight, as the report implies that her activity was restricted and that the caloric intake averaged over 2,300 calories prior to the operation and between 1,600 and 1,900 calories in the postoperative period. The much greater intake of nitrogen and minerals may account for the initial positive balances in Bassett and Alstine's patient, in contrast to the patient reported here. An important feature of both studies is the essential agreement in regard to the direction and magnitude of the shift of the recorded balances after the removal of a functioning parathyroid tumor.

In reviewing the work of Tibbetts and Aub (4) it was noted that Patient O.M. in their report of clinical hyperparathyroidism is similar to the patient reported here. A 13-year-old boy with an intensely active adenoma of the parathryoid glands had serum calcium levels as high as 18.6 and 19.4 mg. per 100 ml. During the preoperative balance studies the intake of calcium was low—0.10 Gm. per day. The weight was constant at 32.5 Kg. over a six-day interval, during which time the average daily balances were: nitrogen +0.18 Gm., magnesium −7.3 mEq., phosphorus −0.44 Gm., and calcium −0.75 Gm. These values approximate those listed in Table 3 for metabolic periods III, IV and V of the present study, except for the nitrogen balance. On the eighth day following the removal of an 11.8-gram parathyroid adenoma in Tibbetts and Aub's patient, a balance study was started which lasted for twelve days. During this period the daily average balances were: nitrogen +5.7 Gm., magnesium +6.8 mEq., phosphorus +0.36 Gm., and calcium +0.56 Gm. The patient gained in weight from 33.1 Kg. to 34.7 Kg., and the serum calcium levels were less than 9.0 mg. per 100 ml. The positive balances were more extreme than those obtained in our study, but the findings in both investigations are essentially in agreement. Any differences may well be a consequence of variation in the individual metabolic pattern of this disease.

SUMMARY

A balance study has been carried out in a patient with hyperparathyroidism in whom two operations were required to remove a hyperfunctioning adenoma.

The first operation provided a control to permit evaluation of the effects of a surgical procedure as such on magnesium balance, apart from the effects of removing a hyperfunctioning parathyroid tumor.

The specific effect of removing the tumor was reversal of previously negative nitrogen, magnesium, phosphorus and calcium balances. The initial loss of magnesium was greater than could be explained by the nitrogen deficit due to the catabolism of soft tissue, and the relatively positive magnesium balance after the removal of the parathyroid tumor could not be explained on the basis of formation of soft tissue with a composition similar to that of normal skeletal muscle. The pronounced renal conservation of magnesium following the removal of the tumor was not due to anesthesia or other features of the surgical procedure. The results of this study conform to a pattern noted in similar cases in the medical literature.

Acknowledgments

The kindness of Dr. Earle M. Chapman in permitting this study of a patient under his care is gratefully acknowledged. The technical assistance of E. B. Gordon and H. Corrigan was invaluable in completing the analyses.

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MUCOPROTEINS IN THYROID AND PARATHYROID DISEASE: CLINICAL AND EXPERIMENTAL STUDIES*

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ALTERATIONS in the level of serum mucoproteins have been reported in a wide variety of unrelated diseases. It has been suggested that these changes are a response to acute and chronic stress due either to an adrenal influence on serum protein formation or to the effect of tissue-breakdown products that contribute to the mucoproteins (1). The purpose of this study is twofold: first, to determine whether stress occasioned by clinical disorders of the thyroid and parathyroid glands can influence significantly the level of the total serum mucoprotein (seromucoid) in man; and second, to investigate the effect of parathyroid extract upon the serum level and the urinary excretion of mucoproteins in the experimental animal.

SUBJECTS AND METHODS

A. *Clinical study*

Patients with hyperthyroidism, myxedema, hyperparathyroidism, and hypoparathyroidism were studied in the untreated state. Upon recovery, a representative number in each group were restudied.

There were 36 patients with hyperthyroidism—33 women and 3 men, 15 to 68 years old. In each, the characteristic clinical picture was associated with an elevated thyroidal uptake of radioactive iodine, a high basal metabolic rate (BMR), and a normal or low level of serum cholesterol.

The 24 patients with myxedema were 33 to 78 years old; there were 17 women and 7 men. In each, the typical clinical picture was associated with a depressed thyroidal uptake of radioactive iodine, a low BMR, and an elevated level of serum cholesterol. Myxedema was primary in 15 patients; it followed thyroidectomy in 6, and radioactive iodine therapy in 3.

The 7 patients with hyperparathyroidism were women, 31 to 53 years old. One presented osteitis fibrosa cystica, 5 renal calculi, and 1 the biochemical characteristics of hyperparathyroidism alone. Hypercalcemia, hypophosphatemia, hypercalciuria, and hyperphosphaturia were demonstrated in all, and the diagnosis was confirmed following surgical removal of a parathyroid adenoma.

The 10 patients with hypoparathyroidism were women, 22 to 57 years old. Each had a low level of serum calcium, a high level of serum inorganic phosphorus, lack of urinary

Received March 20, 1957.

* Supported by a grant from the Drs. Leonard H. and Louis D. Weissman Medical Research Foundation.

calcium (Sulkowitch test), and clinical evidence of latent or frank tetany. Seven were studied shortly after, and 2 several years after, subtotal thyroidectomy. The diagnosis in the remaining patient was idiopathic hypoparathyroidism.

The serum mucoprotein level was determined by turbidimetry (2). Each value represents the mean of determinations on 2 or more fasting morning specimens. Determinations in the immediate postoperative period were excluded. The serum mucoprotein levels in normal old people studied during the same period were 107 ± 18 mg. per 100 ml. for women and 105 ± 18 mg. per 100 ml. for men (3).

B. *Experimental study*

Serum mucoprotein levels were determined by turbidimetry (2) in 16 female Sprague-Dawley rats. Parathyroid extract[1] was administered intraperitoneally in 2 fractional doses. Six animals were given 500 units and 3 were given 1,000 units. The rats were sacrificed at various intervals after the final injection and serum samples were obtained from heart blood. A period of twelve hours was established as the optimal interval for maximal response. Seven other animals sacrificed at the same time served as normal controls.

Urinary mucoprotein excretion was studied in 5 rats in a control and experimental specimen consisting of 2 consecutive 72-hour urine collections. During the first two days of the study period, each animal received parathyroid extract, 500 units, intraperitoneally in fractional doses. Each urine specimen was dialyzed in a cellophane bag against distilled water for forty-eight hours. Perchloric acid (10 *N*) was added to provide a 0.6 *N* concentration to precipitate non-mucoprotein protein. To this was added, after filtering, one fifth of its volume of phosphotungstic-hydrochloric acid reagent. After standing for fifteen minutes, the sample was centrifuged, the supernatant fluid discarded and the precipitate washed with phosphotungstic-hydrochloric acid reagent and with alcohol. The precipitate was dissolved in 0.2 *N* sodium hydroxide and the mucoprotein re-precipitated by phosphotungstic acid. After separation by centrifugation, this precipitate was washed as previously. By use of this procedure, most of the coloring matter was eliminated. The mucoprotein obtained was dissolved in 10 ml. of 0.02 *N* sodium hydroxide and aliquots were taken for determination of different moieties. All procedures were carried out in the cold. Protein content was determined by the biuret reaction (4), tyrosine by the method of Winzler *et al.* (5), carbohydrate by the Orcinol method (6), and phosphate by the method of Fiske and SubbaRow (7).

RESULTS

A. *Clinical study*

Hyperthyroidism (Table 1). The mean mucoprotein level in 36 patients was 101 ± 31 mg. per 100 ml., the range being 66 to 180 mg. Twelve patients were restudied (Table 2) when rendered euthyroid by subtotal thyroidectomy or administration of radioactive iodine. Their mean serum mucoprotein level in the untreated stage was 93 ± 26 mg., and in the euthyroid stage 98 ± 29 mg. per 100 ml. After treatment, the levels were slightly elevated in 8 and depressed in 4 patients.

Myxedema (Table 1). The mean serum mucoprotein level in 24 patients was 102 ± 29 mg. per 100 ml., the range being 68 to 183 mg. In 3 patients in whom the euthyroid state was achieved in four to six months by treatment

[1] Generously supplied by Eli Lilly & Co., Indianapolis, Indiana.

TABLE 1. SERUM MUCOPROTEIN LEVELS IN DISEASES OF THE THYROID AND PARATHYROID GLANDS

Diagnosis	No. of patients	Serum mucoprotein (mg. per 100 ml.)		
		Mean	S.D.*	Range
Hyperthyroidism	36	101	31	66–180
Myxedema	24	102	29	68–183
Hyperparathyroidism	7	127	29	96–168
Hypoparathyroidism	10	110	24	70–139

* In this and subsequent tables, S.D. = standard deviation.

with desiccated thyroid, the mucoprotein level rose by 8, 24, and 41 mg. per 100 ml., respectively. Two patients were rendered euthyroid within two months by administration of triiodothyronine;[2] the mucoprotein level rose by 21 mg. per 100 ml. in one and fell 78 mg. in the other. Thus in these 5 patients the mean before treatment was 117 ± 22 mg. per 100 ml., and afterwards, was 119 ± 12 mg. (Table 2). A single dose of triiodothyronine (25 micrograms) in 3 patients produced no rise in the level of serum mucoprotein determined at four, eight, and twenty-four hours. In a fourth patient, a significant rise occurred, but an attempt to duplicate the effect was unsuccessful.

Hyperparathyroidism (Table 1). The mean serum mucoprotein level in 7 patients was 127 ± 29 mg. per 100 ml., the range being 96 to 168 mg. The highest value observed, 168 mg., was in the patient with osteitis fibrosa cystica; upon recovery, this patient's mucoprotein level was 131 mg. per 100 ml. Five patients with a mean level of 123 ± 27 mg. per 100 ml. before operation had, following the removal of a parathyroid adenoma and res-

TABLE 2. SERUM MUCOPROTEIN LEVELS BEFORE AND AFTER SUCCESSFUL TREATMENT OF DISEASES OF THE THYROID AND PARATHYROID GLANDS

Diagnosis	No. of patients	Serum mucoprotein (mg. per 100 ml.)			
		Before therapy		After therapy	
		Mean	S.D.	Mean	S.D.
Hyperthyroidism	12	93	26	98	29
Myxedema	5	117	22	119	12
Hyperparathyroidism	5	123	27	130	18
Hypoparathyroidism	6	97	22	98	25

[2] Generously supplied (as Cytomel) by the Smith, Kline and French Laboratories, Philadelphia, Pa.

toration of normal serum calcium and phosphorus values, a mean level of 130 ± 18 mg. per 100 ml. (Table 2). The concentration rose slightly in 4 and fell in 1 patient.

Hypoparathyroidism (Table 1). The mean serum mucoprotein level in 10 patients was 110 ± 24 mg. per 100 ml., the range being 70 to 139 mg. Following recovery and restoration of normal serum calcium and phosphorus values by the use of calcium supplements and either vitamin D or dihydrotachysterol, 6 patients with a pretreatment mean of 97 ± 22 mg. per 100 ml. had a mean of 98 ± 25 mg. per 100 ml. The mucoprotein level rose in 4 and fell in 2 patients.

B. *Experimental study*

Serum mucoprotein. In rats, parathyroid extract produced a significant elevation of the serum mucoprotein concentration, proportional to the dose used (Table 3).

Urinary mucoprotein (Table 4). Parathyroid extract did not alter the urinary excretion of mucoprotein. Neither the protein content nor the carbohydrate content of urinary mucoids was significantly affected. The ratio of protein to carbohydrate content remained essentially unchanged. The potency of the parathyroid extract was demonstrated by the marked phosphaturia induced by its administration.

COMMENTS

Recent publications have indicated that the serum level and urinary excretion of mucoproteins are influenced by thyroid and parathyroid disorders or by hormonal products of these glands. Proper evaluation of these reports requires attention to methodology.

The mucoprotein (seromucoid) level of serum measured here designates, as in the studies of Winzler (8), the heterogenous glycoprotein fraction that is soluble in perchloric acid but is precipitated by phosphotungstic acid. This fraction is characterized chemically by strong bonds between carbohydrate and protein moieties. Most methods express the mucoprotein concentration in terms of protein or carbohydrate components of the

TABLE 3. EFFECT OF PARATHYROID EXTRACT UPON THE SERUM MUCOPROTEIN LEVEL OF THE RAT

No. of animals	Dose of parathyroid extract	Serum mucoprotein (mg. per 100 ml.)	
		Mean	Range
7	None	134	104–170
6	500 units	228	180–271
3	1,000 units	276	260–294

TABLE 4. EFFECT OF PARATHYROID EXTRACT UPON THE URINARY EXCRETION OF MUCOPROTEIN AND PHOSPHATE IN THE RAT

Estimation		Animal No.				
		1*	2	3	4	5
Mucoprotein (mg./72 hrs.)						
Tyrosine protein	Before	0.63	0.62	0.84	0.72	0.73
	After†	0.44	0.48	0.66	0.32	0.38
Biuret protein	Before	14.00	13.60	18.60	16.00	16.00
	After	9.50	10.80	14.00	7.10	8.00
Orcinol carbohydrate	Before	1.66	2.15	3.70	1.94	2.10
	After	1.22	1.08	1.94	1.05	0.92
Protein/Carbohydrate ratio	Before	8.5	6.5	4.9	8.5	7.9
	After	7.7	10.00	7.3	6.8	8.7
Phosphate (mg./72 hrs.)	Before	9.60	12.80	5.90	8.10	6.10
	After	27.00	40.90	49.90	21.80	36.50

* Animal died before collection completed. Values represent mg. per 60 hours.

† After 500 units of parathyroid extract daily for the first two days of the second three-day collection period.

complex. By electrophoretic partition, mucroprotein is found in one or more of three separate components which have been thus isolated. Winzler (8) has observed that the ratio of the carbohydrate to the protein content of seromucoid may vary with disease. He states, "It is evident that the question of whether seromucoid levels are normal or abnormal depends upon which constituent of the fraction is determined." The turbidimetric determination circumvents this difficulty, for it provides a measure of the entire mucoprotein complex.

Mustacchi, Petermann and Rall (9) have observed elevated serum mucoprotein levels in hyperthyroidism and low levels in myxedema. Following treatment, the levels changed toward the normal. Mucoprotein was determined as two distinct electrophoretic components. Greenspan (10) reported depressed mucoprotein levels in one fourth of patients with various thyroid gland disorders including hyperthyroidism and myxedema. Wiener *et al.* (11) administered desiccated thyroid to 2 myxedematous subjects and observed a slight rise in serum mucoprotein levels. In these 2 studies, mucroprotein was isolated by the procedure of Winzler and expressed in terms of its protein content.

The skin of a patient with myxedema contains extracellular deposits of a myxomatous material rich in acid-mucopolysaccharides (12). During treat-

ment with thyroid, this substance is mobilized (13). The relationship of tissue acid-mucopolysaccharides to serum mucoproteins, as here defined, has yet to be elucidated (14). Neither desiccated thyroid nor triiodothyronine had a striking effect on the serum mucoprotein level in this study although, in each subject, skin texture became normal. Elucidation of the pathways by which this myxomatous material is eliminated from the body may well require lengthy balance studies.

Engel (15) and Engel and Catchpole (16) observed dissolution of bone matrix, an increase in the serum mucoprotein level, and increased excretion of urinary mucoprotein following the administration of 1,000 units of parathyroid extract to rats. Serum mucoprotein was measured by the method of Winzler and expressed in terms of its carbohydrate-to-tyrosine ratio. Urinary mucoprotein was precipitated with sodium chloride, estimated with Orcinol reagent and expressed in terms of a mannose-galactose standard. That parathyroid extract is also capable of elevating the serum mucoprotein level in man has been shown by previous studies from this laboratory (1). Boyce, Garvey and Norfleet (17) reported that the greatest concentration of urinary mucoprotein found in their experience was that in 2 patients with hyperparathyroidism. Their method recovered urinary biocolloids by combining dialysis, ultrafiltration and perevaporation. A single mucoprotein electrophoretic fraction was then determined in the salt-soluble biocolloid fraction.

The lack of correlation between the data of these reports and their variance from findings reported here most probably reflects the heterogeneity of serum and urinary mucoproteins and the difficulties inherent in the isolation, determination and expression of the total complex in terms of its various constituents. The possibility remains that one fraction of the mucoprotein complex may vary without significantly influencing the whole. It is also possible that the experimentally observed effect of parathyroid extract on mucoproteins may reside in a fraction of the hormone related to, or independent of the phosphaturia-inducing fraction; or it may be an artefact of the extract.

The present study thus demonstrates that the concentration of total serum mucoprotein is not significantly influenced by the clinical disorders of the thyroid and parathyroid glands studied. Furthermore, although administration of parathyroid extract resulted in elevation of the serum mucoprotein level in the rat, no increase in the urinary excretion of mucoprotein could be demonstrated by the methods used.

SUMMARY

The serum mucoprotein level, determined turbidimetrically in patients with hyperthyroidism, myxedema, hyperparathyroidism and hypoparathyroidism, before and after treatment, was not significantly altered from

normal values. Parathyroid extract, administered to rats, raised the serum mucoprotein level as determined by turbidimetry without increasing the urinary excretion of mucoprotein similarly measured.

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THIRTY-ONE MEN WITH FEMALE SEX CHROMATIN

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DETERMINATION of the sex chromatin pattern is being more and more widely used in the examination of patients with various disturbances of somato- or psychosexual development. In 1956 this method of investigation showed that sex chromatin was of the feminine type in 18 cases of so-called Klinefelter's syndrome (1–5).

Jirásek and Raboch (6) examined smears of the oral mucosa in 167 males with disturbances in genital development. The series included cases of hypospadias, bilateral aplasia of the ductus deferens, undescended testes, and sterility associated with absent or arrested spermatogenesis. In the course of that work, they found that the sex chromatin was usually of the female type only in patients with small testes (about 2 cm., long axis). For that reason they instituted a program of re-examining all men in whom, during the previous few years, small testes had been found by palpation, even though biopsy and other laboratory investigations had not been performed.

Forty-four such men were re-examined. In 31 of these the sex chromatin was of the female type—Group I—and in 11 of these, biopsy revealed thickening and hyalinosis of basal membranes. The remaining 13 patients had hypogonadotropic eunuchoidism (proved by testicular biopsy or by estimation of urinary gonadotropin) and the sex chromatin was always of the male type—Group II.

In this paper we shall evaluate some of the findings in these two groups of men, in whom the hormonal activity of the gonads was often deficient.

METHODS

Somatic measurements were made in all 44 patients. As suggested by Hynie, in addition to the height and weight, the following proportions were measured by means of an adjusted pelvimeter in patients lying on a horizontal examination table: the length of the trunk, the length of the ulna, the biacromial distance, and the bitrochanteric distance.

The long axis of the testis was measured by means of a testimeter, as suggested by Hynie. In men with a normal ejaculate, the long axis is usually greater than 3.4 cm. (7). The clinical and spermatologic examinations were always performed by the same person. Testicular biopsy specimens were fixed in Bouin solution and stained with hematoxylin-eosin; the microscopic examinations were made by Dr. Záhoř. Sex chromatin

Received January 10, 1957.

was determined in smears of the buccal mucosa; the samples were prepared by a method developed by Dr. Jirásek (8) and were evaluated by him without any personal knowledge of the patient or of the results of the clinical examination. Quantitative determination of urinary gonadotropin was carried out by Dr. Štěrba, using a biologic test on infantile male rats.

CLINICAL MATERIAL

Group I. Sex chromatin of the female type, associated in about a third of the cases with thickening and hyalinosis of the testicular basement membrane. The ages of the 31 men ranged from 20 to 49 years (average, 31 years).

Group II. Sex chromatin of the male type, associated with hypogonadotropic eunuchoidism. The ages of the 13 men ranged from 20 to 42 years (average, 30 years).

Controls. In each case a comparison of somatic measurements was made with the average values for normal males of the same height, gained by an examination of 500 healthy men from sterile marriages (9). All of these men reported a normal course and adequate frequency of sexual life. On palpation, their genitalia were invariably normal. Examination of the ejaculate yielded normal findings: there was always more than 1.5 cc. of spermatic fluid, the number of spermatozoids per cc. was always greater than 40 million, their motility was normal, and the proportion of morphologically defective forms was less than 30 per cent. The average values for the somatometric proportions relating to the different body heights of these normal men are listed in Table 1.

The difference in values between the normal men and the patients from Groups I and II was expressed in the appropriate standard deviation. Values which fell within the range from -1.00 to $+1.00$ were regarded as normal.

RESULTS

In Tables 2 and 3 respectively are listed the somatic, testicular and penile measurements in the 31 patients with female-type sex chromatin, and in the 13 hypogonadotropic eunuchoids with male-type chromatin.

In Table 4, a general comparison is made of the results of somatic measurements in Groups I and II.

Height. In both groups the patients were often taller than normal.

Weight. There was a trend toward low weight values in both groups, but it was more pronounced in Group I.

Length of trunk. This is a basic anthropometric measurement. In both groups there was a pronounced trend towards minus values, slightly more accentuated in Group II. In the majority of the patients, the length of the trunk was significantly shorter than normal.

TABLE 1. AVERAGE VALUES OF SOME SOMATOMETRIC PROPORTIONS IN NORMAL MEN. THE AVERAGE HEIGHT FOR THE WHOLE GROUP OF 500 MEN WAS 172.3 CM. AND THE AVERAGE WEIGHT WAS 72.5 KG.

Height (cm.)	Weight (Kg.)	Length of trunk (cm.)	Double length of ulna (cm.)	Biacromial distance (cm.)	Bitrochanteric distance (cm.)
160	63.69	49.6	50.0	37.9	31.1
161	64.41	49.8	50.3	38.0	31.2
162	65.12	50.1	50.6	38.1	31.3
163	65.84	50.3	50.9	38.2	31.5
164	66.55	50.5	51.2	38.3	31.6
165	67.26	50.8	51.5	38.4	31.8
166	67.98	51.0	51.7	38.6	31,9
167	68.69	51.3	52.0	38.7	32.0
168	69.41	51.5	52.3	38.8	32.2
169	70.12	51.8	52.6	38.9	32.3
170	70.83	52.0	52.9	39.0	32.5
171	71.55	52.2	53.1	39.1	32.6
172	72.26	52.5	53.4	39.2	32.8
173	72.98	52.7	53.7	39.4	32.9
174	73.69	53.0	54.0	39.5	33.0
175	74.40	53.2	54.3	39.6	33.2
176	75.12	53.4	54.5	39.7	33.3
177	75.83	53.7	54.8	39.8	33.5
178	76.55	53.9	55.1	39.9	33.6
179	77.26	54.2	55.4	40.1	33.7
180	77.98	54.4	55.7	40.2	33.9
181	78.69	54.7	55.9	40.3	34.0
182	79.40	54.9	56.2	40.4	34.2
183	80.12	55.1	56.5	40.5	34.3
184	80.83	55.4	56.8	40.6	34.4
185	81.54	55.6	57.1	40.7	34.6

Length of ulna. In Group I, on the whole, the distribution of values was equal among all four categories. In Group II, there was a trend toward plus values. In hypogonadotropic eunuchoids, the ulna is often longer than in normal men.

Biacromial distance. This is a basic anthropometric measurement. In both groups there was a marked trend towards minus values. Most of the patients were narrower in the shoulders than normal men.

Bitrochanteric distance. In Group II, the values for bitrochanteric distance revealed a trend toward wide hips, a tendency that was not observed in Group I.

Long axis of testis. In Group I the long axis of each testis was between 1.0 cm. and 2.6 cm., and in Group II it was between 1.0 cm. and 2.0 cm.

TABLE 2. SOME SOMATOMETRIC VALUES AND CLINICAL FINDINGS IN 31 MEN WITH FEMALE-TYPE SEX CHROMATIN

Patient	Age (yrs.)	Height (cm.) & S.D.*	Weight (Kg.)	Length of trunk (cm.)	Double length of ulna (cm.)	Biacromial distance (cm.)	Bitrochant. distance (cm.)	Size of penis (cm.)	Testicular long axis (cm.)	
									Left	Right
1. L.M.	46	160 −1.99	53 −1.31	49 −0.37	50 0.0	36 −1.31	29 −1.69	7.6×2.3	1.8	1.8
2. K.J.	49	161 −1.83	71 +0.81	47 −1.72	53 +1.59	32 −4.17	33 +1.45	5.0×2.0	1.0	1.0
3. T.J.	30	169 −0.54	63 −0.87	50 −1.11	53 +0.23	37 −1.31	30 −1.85	8.4×2.5	1.8	1.8
4. S.M.	30	171 −0.21	58 −1.66	51 −0.74	52 −0.65	38 −0.76	32 −0.48	6.8×2.4	2.0	2.0
5. K.R.	20	177 +0.76	73 −0.35	51 −1.66	54 −0.47	38 −1.24	30 −2.82	8.0×2.6	2.0	2.0
6. K.V.	44	177 +0.76	77 +0.14	45 −5.37	60 +3.07	39 −0.55	34 +0.40	7.5×2.5	1.5	1.5
7. N.Z.	26	177 +0.76	71 −0.59	51 −1.66	56 +0.70	38 −1.24	33 −0.40	8.0×2.5	2.0	1.8
8. F.O.	22	179 +1.08	68 −1.14	51 −1.97	55 −0.24	36 −2.85	34 +0.24	6.0×2.0	2.0	2.0
9. H.D.	24	180 +1.25	67 −1.35	52 −1.48	58 +1.36	39 −0.83	34 +0.08	8.8×3.0	2.2	2.2
10. O.J.	21	180 +1.25	63 −1.84	51 −2.10	58 +1.36	35 −3.61	33 −0.73	6.2×2.4	2.0	1.8
11. B.V.	25	182 +1.57	61 −2.26	52 −1.78	54 −1.30	33 −5.14	33 −0.97	7.6×2.6	2.0	2.0
12. K.A.	27	183 +1.73	74 −0.75	53 −1.29	56 −0.29	40 −0.34	34 −0.24	9.2×3.0	2.0	1.8
13. K.J.	34	184 +1.89	85 +0.51	56 +0.37	52 −2.84	36 −3.20	36 +1.29	6.6×2.4	1.5	1.5
14. M.V.	31	190 +2.87	73 −1.30	52 −2.95	60 +0.88	39 −1.52	35 −0.16	7.6×2.8	bilateral cryptorchidism	
15. V.J.	27	165 −1.19	50 −2.11	47 −2.34	52 +0.29	35 −2.35	32 +0.16	6.4×2.2	2.5	2.5
16. C.Z.	25	166 −1.02	64 −0.48	51 0.0	49 −1.59	40 +0.96	31 −0.72	6.2×2.2	2.0	2.0
17. B.P.	28	166 −1.02	74 +0.86	49 −1.23	54 +1.35	39 +0.27	32 +0.08	8.2×2.1	2.2	2.2
18. T.K.	34	170 −0.37	71 +0.02	52 0.0	50 −1.71	36 −2.08	32 −0.40	7.6×2.2	1.5	2.5
19. F.V.	32	177 +0.76	62 −1.70	54 +0.18	56 +0.70	36 −2.63	32 −1.21	8.4×2.4	2.0	2.0

* The standard deviation expresses the difference from the average values found in normal men.
Note: Cases Nos. 14, 24 and 31 were evaluated on the basis of results of hitherto unpublished data.

TABLE 2—*Continued*

Patient	Age (yrs.)	Height (cm.) & S.D.*	Weight (Kg.)	Length of trunk (cm.)	Double length of ulna (cm.)	Biacromial distance (cm.)	Bitrochant. distance (cm.)	Size of penis (cm.)	Testicular long axis (cm.)	
									Left	Right
20. S.M.	33	178 +0.92	92 +1.89	53 −0.55	54 −0.64	41 +0.75	34 +0.32	7.8×2.5	2.5	2.6
21. W.O.	28	178 +0.92	77 +0.05	52 −1.17	55 −0.05	36 −2.70	33 −0.48	8.2×2.6	2.0	2.3
22. S.L.	25	183 +1.73	67 −1.61	51 −2.52	57 +0.29	38 −1.73	33 −1.05	9.0×2.6	2.0	2.2
23. Š.J.	38	185 +2.05	89 +0.91	56 +0.24	54 −1.83	38 −1.87	35 +0.32	5.8×2.6	2.3	2.3
24. K.J.	42	189 +2.70	77 −0.72	54 −1.53	62 +1.84	36 −3.53	37 +1.53	10.7×3.0	1.8	1.8
25. S.J.	33	160 −1.99	60 −0.44	49 −0.37	49 −0.59	34 −2.70	29 −1.69	9.4×2.4	2.0	2.0
26. K.M.	34	161 −1.83	65 +0.07	47 −1.72	50 −0.17	37 −0.69	30 −0.97	4.8×2.2	2.0	2.0
27. V.B.	30	170 −0.37	82 +1.37	51 −0.62	50 −1.71	36 −2.08	32 −0.40	7.4×3.0	2.0	2.0
28. S.Z.	28	176 +0.60	63 −1.48	52 −0.86	55 +0.29	38 −1.17	32 −1.05	6.8×2.4	2.0	2.2
29. H.J.	32	177 +0.76	81 +0.63	51 −1.66	55 +0.11	38 −1.24	33 −0.40	8.4×2.4	2.0	2.0
30. Ž.V.	36	182 +1.57	73 −0.78	53 −1.17	60 +2.25	39 −0.96	34 −0.16	9.4×3.0	2.0	1.8
31. R.R.	28	192 +3.19	70 −1.88	54 −1.91	62 +1.83	38 −2.35	35 −0.32	8.0×2.2	2.0	2.0

Bilateral cryptorchism was noted in 1 patient of Group I. The testes in both groups were obviously hypoplastic, and in Group II they were somewhat smaller than in Group I.

Length of penis. In Group I the penis was longer than 6 cm. in 28 patients, and shorter than 6 cm. in only 3 patients; the average length was 7.6 cm. In Group II the penis was shorter than 6 cm. in 9 patients, and 6 cm. or longer in only 4 patients (treated hormonally elsewhere); the average length was 5.0 cm. In most patients of Group I the penis was adequately developed, whereas in most patients of Group II it was subnormal in size.

Gynecomastia. In Group I, gynecomastia was found in 11 patients; it was bilateral in 9 and unilateral in 2. In the 13 patients of Group II, bilateral gynecomastia was found in 7.

Beard and pubic hair. Only 4 men in Group I had an ample beard; 8 had

a very scanty beard or almost none; and 19 had a growth of hair which was ample, but limited to a fringe around the mouth. In Group I the upper line of pubic hair growth was horizontal in 6; some hair reached as high as the navel in 8; and the distribution was obviously virile in the remaining 17. In Group II, on the other hand, all 13 patients had either no beard or only fuzz. The upper line of pubic hair growth was always horizontal.

Ejaculate. No spermatozoids were found in the spermatic fluid of any patient of either group.[1] The patients of Group I were divided into 3 subgroups, according to the quantity of ejaculate:

a) less than 1.5 cc.—14 cases (Table 2, Nos. 1–14)

b) 1.5 to 3.0 cc.—10 cases (Table 2, Nos. 15–24)

c) over 3.0 cc., up to 7.9 cc.—7 cases (Table 2, Nos. 25–31)

All 13 patients in Group II had less than 1.5 cc. of ejaculate. In 6 there was no spermatic fluid, and in 7 only one or two drops.

Testicular biopsy. In Group I, biopsy was performed in 7 patients in subgroup *a*, 3 patients in subgroup *b*, and 1 patient in subgroup *c*. In the histopathologic picture, thickening and hyalinosis of the basal membrane of the tubules was conspicuous. Single tubules in 2 patients contained cells of seminiferous epithelium—spermatogonia, spermatocytes and even spermatids. The Leydig cells were relatively increased and appeared abnormal functionally. In Group II, 8 patients had testes which resembled those of the prepuberal period. The germinal epithelium was always immature, and there were no Leydig cells.

Sex chromatin. Sex chromatin was of the female type in all 31 cases of Group I. It was invariably of the male type in the 13 hypogonadotropic eunuchoids comprising Group II.

Sex life. In Group I, 21 of the 31 men (67 per cent) were married, 2 were divorced, and 8 were single. Of the 21 married men, 19 reported a normal course of sexual relations, the frequency of which was between three times a week and three times a month. In subgroup *a* (less than 1.5 cc. of ejaculate) there were 2 married men whose libido was very weak: in one (aged 46) coitus took place once every two weeks, and in the other (aged 49) about once every three months. In subgroup *a* were 6 bachelors aged 20 to 30 years; 3 of them reported that they were not at all interested in women. The other 2 bachelors in Group I belonged to subgroup *b;* they were capable of coitus in chance love affairs.

In Group II, 8 of 13 patients (61 per cent) were single. All stated that their libido was weak. The development of sociosexual relations was fur-

[1] We have examined a total of 40 men with female sex chromatin. In one of our recent patients (V.V., 31 years old), three different examinations of the semen showed the presence of single spermatozoids, some of which had slight motility. The amount of spermatic fluid was always more than 3.0 cc.

TABLE 3. SOME SOMATOMETRIC VALUES AND CLINICAL FINDINGS IN 13 HYPOGONADOTROPIC EUNUCHOIDS

Patient	Age (yrs.)	Height (cm.) & S.D.*	Weight (Kg.)	Length of trunk (cm.)	Double length of ulna (cm.)	Biacromial distance (cm.)	Bitrochant. distance (cm.)	Size of penis (cm.)	Testicular long axis (cm.)	
									Left	Right
1. H.V.	42	162 −1.67	69 +0.47	48 −1.29	52 +0.82	36 −1.45	33 +1.37	5.8×2.0	1.0	1.0
2. L.A.	36	164 −1.35	66 −0.06	46 −2.77	52 +0.47	35 −2.29	33 +1.13	2.2×1.2	2.0	0
3. H.K.	27	167 −0.86	63 −0.69	47 −2.64	54 +1.18	38 −0.48	34 +1.61	6.0×2.0	1.0	1.0
4. H.J.	25	169 −0.54	60 −1.24	49 −1.72	54 +0.82	33 −4.09	33 +0.56	3.6×1.5	1.8	1.6
5. B.V.	30	170 −0.37	86 +1.86	51 −0.62	54 +0.65	38 −0.69	33 +0.40	4.2×2.0	2.0	1.8
6. O.Š.	32	174 +0.27	86 +1.51	51 −1.23	56 +1.18	38 −1.03	36 +2.42	3.5×2.0	2.0	1.0
7. M.S.	24	175 +0.43	58 −2.01	47 −3.82	53 −0.76	32 −5.27	32 −0.97	5.4×2.0	1.6	1.6
8. G.J.	35	178 +0.92	79 +0.30	50 −2.40	61 +3.49	37 −2.02	39 +4.35	5.0×2.0	1.5	1.5
9. T.J.	26	179 +1.08	72 −0.64	51 −1.97	55 −0.24	38 −1.46	34 +0.24	7.0×2.5	2.0	2.0
10. M.J.	20	179 +1.08	73 −0.52	52 −1.35	56 +0.35	35 −3.53	34 +0.24	5.0×2.0	2.0	2.0
11. M.J.	33	180 +1.25	74 −0.49	53 −0.86	59 +1.95	38 −1.52	38 +3.30	5.6×2.2	1.0	1.0
12. T.E.	32	182 +1.57	96 +2.04	57 +1.29	60 +2.25	36 −3.05	36 +1.45	6.0×2.0	1.0	1.0
13. Ž.V.	29	184 +1.89	61 −2.44	50 −3.33	60 +1.89	36 −3.19	34 −0.32	6.0×2.0	2.0	2.0

* The standard deviation expresses the difference from the average values found in normal men.

th.r inhibited through feelings of inferiority allegedly evoked by their realization that their genitals were inadequately developed. Five patients of Group II were married. Most of them reported an adequate frequency of sexual relations; 4 had coitus once or twice a week, and 1 twice a month. Nevertheless, they complained of reduced libido, weak sensations accompanying coitus, and lack of ejaculation.

DISCUSSION

Comparison of the foregoing findings revealed differences between Groups I and II and also between these groups and a group of normal men.

TABLE 4. COMPARISON OF SOMATIC MEASUREMENTS IN GROUPS I AND II

	No. of Patients in Whom Standard Deviation was			
	less than −1	−1 to 0	0 to +1	over +1
		Height		
Group I	7	4	8	12
Group II	2	3	3	5
		Weight		
Group I	12	8	9	2
Group II	3	5	2	3
		Length of trunk		
Group I	20	7	4	0
Group II	10	2	0	1
		Length of ulna		
Group I	6	9	8	8
Group II	0	2	5	6
		Biacromial distance		
Group I	22	6	3	0
Group II	11	2	0	0
		Bitrochanteric distance		
Group I	7	14	7	3
Group II	0	2	4	7

There was obvious hypoplasia of the testes in patients of both Groups I and II. Most of the men in Group I had a well developed penis, and the growth of hair on the body was more widespread than that of Group II patients, in whom the penis was usually of subnormal size and the growth of hair very sparse. The quantity of spermatic fluid in Group I ranged from 0 to 7.9 cc.; in Group II, without treatment, the quantity was always subnormal—less than 1.5 cc. Differences were also observed in the development of sociosexual relations and in the course of sexual life.

For the time being, it is impossible to provide a detailed and accurate explanation of the relationship between female-type sex chromatin and the degenerative processes in the testes which cause thickening and hyaline

degeneration of tubules and even their obliteration, as well as various degrees of damage to the Leydig cells. In a previous paper (6) we showed that a similar histopathologic picture may be induced by other pathologic influences—for example, those acting in cryptorchism or in deficient vascular supply as seen in some varicoceles. However, in these cases the sex chromatin has been of the male type. Nelson (10) distinguishes between "true Klinefelter syndrome" with a female nuclear pattern and "false Klinefelter syndrome" with male-type sex chromatin.

The growth processes in Groups I and II took a different course from that in normal individuals. The length of the trunk and the biacromial distance were usually less than in healthy men. Raboch and Malý (9) found the same trend in these fundamental anthropometric values in 350 men with hypoplastic testes and in 130 cases of cryptorchism; they believed it to be a sign of retardation of the developmental processes during adolescence in consequence of disturbed hormonal balance. In the hypogonadotropic eunuchoids of Group II (whose supply of androgens during the puberal period was presumably on a still lower level than that of the men in Group I), there was a trend toward increased length of the ulna and of the bitrochanteric distance compared with these measurements in normal men.

The presence of even a reduced quantity of testicular secretion during adolescence, though it may be transient, is sufficient for the stimulation of the growth of the penis—a tissue very sensitive to androgens. This may explain the size of the penis in the patients of Group I. In the same way one can explain the more widespread growth of hair in these men. In many of them the finding of an ample growth of hair forming a fringe around the mouth but sparsity or absence of hair on the cheeks, seems to be characteristic. In Group II, the small penis and the eunuchoid distribution of pubic hair indicate a permanently deficient supply of androgen.

Further experience will show whether or not determination of sex chromatin (either in the cells of the buccal mucosa or in neutrophil leukocytes of the blood) can be used in the differential diagnosis of certain hyper- and hypogonadotropic states. The procedure would have to be relatively simple, inexpensive, and painless.

From the foregoing study, 2 complexes are delineated:

1. *Hypergonadotropic syndrome, i.e.,* obviously hypoplastic testes+penis of normal length+often a characteristic growth of hair around the mouth +female sex chromatin.

2. *Hypogonadotropic eunuchoidism, i.e.,* obviously hypoplastic testes +penis of subnormal length (without treatment)+eunuchoid distribution of pubic hair+male sex chromatin.

It is evident that it is not possible to include *all* men with distinct hypoplasia of the testes sometimes combined with disturbance of hormonal

activity, into one of the 2 foregoing complexes. We have seen several men with small testes and no pronounced signs of endocrine disturbance who had male-type sex chromatin. In these cases, a developmental disturbance of the male sex glands may have occurred either during late fetal life or prepuberally. Moreover, in a "fertile eunuchoid" whom we examined, the nuclear pattern was of the male type but the urinary gonadotropin was elevated. On the basis of our experience so far, however, we believe that a preliminary diagnosis in most cases of male eunuchoidism is possible by means of the simple test for sex chromatin in smears of the buccal mucosa, and that such determinations aid in the course of further investigation and possible therapy.

Most of the patients in Group I were married and capable of coitus. Their principal problem was sterility. In Group II, on the other hand, most of the patients were single. All of them reported weak libido, and psychosexually they were further inhibited by feelings of inferiority resulting from their inadequate development. The lack of testicular androgens thus inhibited their somato- and psychosexual maturation by both direct and indirect effects connected with their realization of developmental inadequacies. The patients of Group II who were married complained of unsatisfactory intercourse characterized by weak libido, poor sensual satisfaction during coitus, and a feeling that there had been no ejaculation. The observations in both groups seem to indicate that lack of testicular androgens intervenes more effectively and distinctly with the development and course of sex life than do factors leading to the formation of female-type sex chromatin.

SUMMARY

Some clinical and laboratory findings in 31 men with female-type sex chromatin (Group I) have been evaluated, and a comparison made with the results of a similar investigation in 13 hypogonadotropic eunuchoids (Group II) in whom the sex chromatin was of the male type.

Differences were observed in certain growth measurements—lengths of the trunk and of the ulna, and biacromial and bitrochanteric distances—the size of the penis, the type of hair growth, and the development and course of sexual life.

Obvious hypoplasia of the testes (long axis, 2 cm.) was invariably found in all patients of both groups. In 11 of the 31 patients in Group I, testicular biopsy showed a histopathologic picture regarded as typical for so-called Klinefelter's syndrome; in 8 of the 13 hypogonadotropic eunuchoids in Group II, the picture was that of prepuberal testes.

The quantity of spermatic fluid in patients of Group I ranged from 0 to 7.9 cc.; in approximately half the cases, the amount was less than 1.5 cc. In Group II, there was always less than 1.5 cc. of ejaculate.

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ESTROGEN EXCRETION LEVELS IN THE NORMAL POSTMENOPAUSAL WOMAN

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THE cessation of menstruation at the time of the menopause is not invariably accompanied by atrophic changes in the genital tract. Moreover the speed of the onset of atrophy and its completeness vary greatly in different individuals and even in different parts of the genital tract of the same woman. Novak and Richardson (1) found active hyperplasia and proliferation of the endometrium in patients many years past the menopause. In a series of patients studied by the author previously (2) it was shown that atrophic changes were present in over 95 per cent. In many instances the atrophy was accompanied by cystic changes in the glands, either diffusely throughout the endometrium or in a polyp of the senile type. In the remaining cases the endometrium exhibited hyperplasia or proliferation and in 1 case a secretory pattern was noted.

Endometrial activity is generally assumed to be the result of ovarian hormone secretion, particularly of estrogen. In view of the varying endometrial patterns, some writers have tried to demonstrate possible continued action of estrogens in the normal postmenopausal woman. Mack (3), using the glycogen content of the vaginal cells as an index of estrogenic activity, estimated that in 30 per cent of elderly women there was evidence of continued estrogen secretion. Previously Robson *et al.* (4) by bioassay methods found estrogens in the urine of postmenopausal women. The picture was complicated by reports that estrogens could be demonstrated by biologic methods in the urine of surgically castrated women. The inference was that estrogens, if present, were not of ovarian origin.

Ovarian estrogens are generally assumed to follow a well-defined metabolic pattern involving estradiol-17β, estriol and estrone. Brown (5) recently described an accurate and apparently specific chemical method for separately estimating these substances in human urine. He reported the finding of small quantities in the urine of postmenopausal women.

It was therefore decided to study a series of normal elderly women, using Brown's method, in an attempt to correlate the chemical findings with the histologic appearances of the endometrium. This is obviously necessary before considering the findings in patients suffering from postmenopausal bleeding or endometrial carcinoma.

Received March 25, 1957.

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Moreover, Fluhmann and Murphy (6) claimed to have demonstrated cyclic variations in the level of blood estrogens in normal postmenopausal women. We wished to check this finding.

CLINICAL MATERIAL AND METHOD

The 24-hour urinary output of estrogens was estimated twice weekly in a series of 7 normal elderly postmenopausal women (average age, 59 years) over a period of from six to eight weeks. The average time after the menopause was 10.3 years, the range being from two to twenty-six years.

In 6 patients a repair operation for prolapse was performed and a routine curettage preceded the operation. The seventh patient was treated by vaginal hysterectomy, with conservation of both ovaries. Following the operation the patients were studied for an average of seven weeks. None of the patients had suffered from postmenopausal bleeding. Apart from the symptoms of prolapse, none had any complaints referable to the genital tract. Complete 24-hour specimens of urine were collected and analyzed.

RESULTS

Estrogen Excretion in Normal Postmenopausal Women

The total amount of estrogens was very small—roughly about the same as that found in women of the child-bearing period of life at the time of menstruation, when ovarian activity is generally assumed to be at its lowest in the cycle. There was no evidence of any cyclic variation, although the amounts varied considerably from time to time, not only in total estrogen but in the individual fractions. The variations in total estrogens occurred irregularly and over relatively short periods of time. Successive estimations sometimes showed little or no estrogens in one specimen, followed by a significant increase in a second estimation carried out three days later. Detailed analysis, not only of the total estrogens, but also of the individual fractions did not reveal any distinct pattern of excretion, either in the group or in the individual patient (Fig. 1).

The estradiol levels were almost invariably low and frequently nil. The average excretion was 0.6 μg. per twenty-four hours. There was 1 notable exception—a patient aged 71 years, who was twenty-six years past the menopause, on one occasion excreted 5.6 μg. The highest fractional values were for estriol, the average output of which was just over 3 μg. per twenty-four hours. For this fraction also there were a few zero readings, although this was not observed so frequently as with the estradiol fraction. The highest output occurred in a patient aged 57 who was twelve years past the menopause, the value being 10.8 μg. per twenty-four hours. The average excretion of estrone was approximately 2 μg. in the 24-hour specimen. Zero values were not so frequent as in the case of estradiol but occurred more

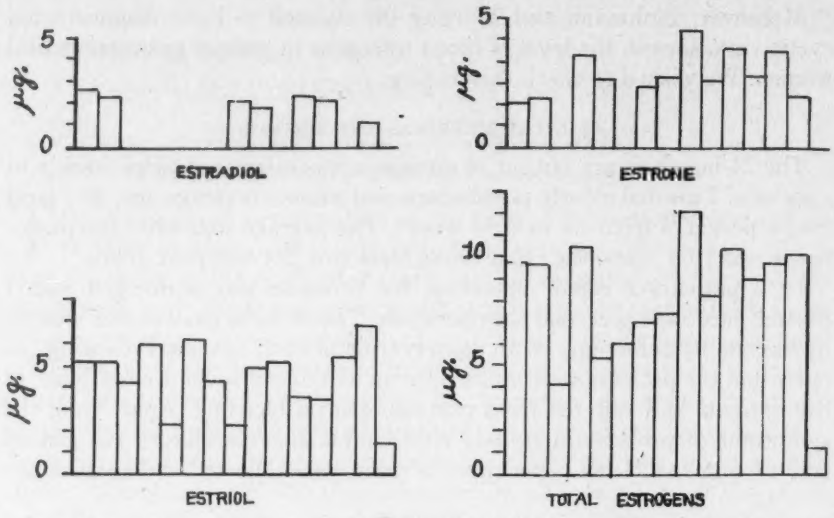

FIG. 1. Variations in the 24-hour urinary excretion of total estrogens and components in a woman aged 56 (para 1) four years past the menopause. Operation—vaginal hysterectomy. The uterus was atrophic. Histology—simple atrophy of the endometrium. Estimations were made at three-day intervals over a period of about seven weeks.

commonly than with estriol. The highest 24-hour output of estrone was shown by the patient aged 57, and was 7.2 μg. Generally, the estrone level was about half to two thirds of the estriol level. The results are shown in Table 1.

All 7 patients had an atrophic endometrium, but in 1 case a senile endometrial polyp was also obtained at the time of curettage.

TABLE 1. ESTROGEN EXCRETION BY NORMAL POSTMENOPAUSAL WOMEN
(μg. per 24 hrs.)

No.	Estradiol	Estriol	Estrone
1	0.6 (0–1.7)*	3.5 (0–6.1)	2.3 (0–4.1)
2	1.0 (0–2.6)	4.4 (1.3–6.7)	2.7 (0–5.4)
3	0.2 (0–1.8)	3.3 (0–10.8)	2.5 (0–7.2)
4	1.1 (0–5.6)	5.4 (0.8–8.0)	1.5 (0–4.8)
5	0.3 (0–1.3)	2.4 (0–5.6)	1.7 (0–4.2)
6	0.5 (0–2.9)	2.8 (0–6.4)	1.1 (0–4.0)
7	0.4 (0–2.7)	1.6 (0–3.8)	1.1 (0–3.6)

* Values are the mean; in parentheses, the range.

Correlation of Estrogen Excretion and Endometrial Histology

It is known that proliferation and hyperplasia of the endometrium may be present in the asymptomatic postmenopausal woman. As atrophy of the senile endometrium is thought to be closely related to the withdrawal of estrogen at the time of the menopause; it seemed advisable to correlate the level of estrogen excretion with the endometrial pattern in an additional series of cases. Since no cyclic variation in the level of urinary estrogen was noted in the foregoing study, it was considered that estimations on single 24-hour specimens would furnish reliable information on this point.

Simple atrophy of the endometrium

The 38 patients in this group were two to twenty-four years past the menopause. The degree of atrophy of the endometrium bore no relationship to the length of time since the menopause. Atrophic changes were as complete in the early years after the cessation of menstruation as in the elderly woman. For the most part the patients were operated on because of the presence of prolapse and in 3 instances atrophic changes were noted in the vagina. In 1 case the menopause had been induced seven years previously by deep x-ray therapy for menopausal menorrhagia.

All but 1 of the patients were parous, but as prolapse was the indication for operation the preponderance of parous patients was not unexpected. In 13 cases, the endometrium was noted on histologic examination to be atrophic—the glands were small and infrequent, the stroma was dense and the general appearances inactive. In 25 patients careful curettage of the uterus failed to produce any endometrium—a circumstance which indicated endometrial atrophy.

The total daily excretion of estrogens varied from 1.4 μg. to 22.0 μg. The low excretion was in the patient who was twenty-four years past the menopause, and the high excretion was in a patient whose last menstrual period was only two years previously.

This relationship between date of the menopause and level of estrogen excretion was not found in the other cases in this group. In each instance estriol accounted for from a half to two thirds of the total estrogen excreted and in 2 cases was the only estrogen detected.

Cystic atrophy of the endometrium

In 8 cases, when curettage was performed the material obtained was more bulky than normal and in several instances an endometrial polyp was noted. Histologic examination showed the presence of cystic dilated glands with an inactive and fibrous stroma. A polyp exhibiting these char-

acteristics is termed a senile endometrial polyp and it is considered that this endometrial pattern is one of cystic atrophy.

The range of 24-hour estrogen excretion in this group was from 3.3 μg. to 17.7 μg. The patients were from four to twenty-one years past the menopause and were all parous. There was no significant difference between the cases in which curettage showed a senile endometrial polyp and the cases of diffuse cystic atrophy. Estriol was by far the highest fraction, frequently accounting for two thirds to three quarters of the total, and on one occasion forming the total estrogen excretion for twenty-four hours. The amount of estradiol and estrone excreted was extremely low and there was no constant relationship between the two factors. Sometimes one was greater and sometimes the other, but the amounts were so small that no significance could be attached to these variations.

Cystic glandular hyperplasia

There were 4 cases of cystic glandular hyperplasia of the endometrium occurring in postmenopausal patients who were not suffering from bleeding.

In view of the special interest of these cases the values for 24-hour estrogen excretion are listed:

	Patient 1	Patient 2	Patient 3	Patient 4
Estrone	Nil	2.79 μg.	Nil	Nil
Estradiol	Nil	3.1 μg.	3.7 μg.	4.6 μg.
Estriol	16.8 μg.	14.73 μg.	15.06 μg.	11.2 μg.
Total estrogens	16.8 μg.	20.62 μg.	18.76 μg.	15.8 μg.

It will be seen that the total estrogens excreted were higher than the average levels for patients in whom the endometrium showed an atrophic pattern. On the other hand the amount of estrogens did not exceed the highest levels seen in the cases of atrophic endometrium. As in the other groups, estriol formed the large proportion of total estrogen—in 1 case equalling the total.

Before and after oophorectomy

In several cases it was possible to determine estrogen excretion before and after oophorectomy. Two patients who had not experienced postmenopausal bleeding excreted 7.5 μg. and 19.2 μg. of total estrogens in twenty-four hours. Two other patients had undergone hysterectomy and bilateral oophorectomy because of postmenopausal bleeding associated with cystic glandular hyperplasia; total estrogen excretions three weeks after operation were 9.6 μg. and 6.1 μg. In 3 cases of endometrial carcinoma a hysterectomy

and bilateral salpingo-oophorectomy had been performed; three weeks after operation the estrogen excretion levels were 17.4 μg., 5.2 μg. and 11.2 μg.

DISCUSSION

A considerable amount of clinical and experimental evidence has been adduced to show that endometrial hyperplasia is closely related to estrogen production. Initially it was taken for granted that these estrogens were invariably of ovarian origin, but the occurrence of endometrial hyperplasia in postmenopausal patients set a problem which cannot be so easily answered. After the menopause the ovary no longer undergoes the cyclic changes resulting in the production of Graafian follicle and corpus luteum, the structures considered by many to be the source of estrogens during the menstrual cycle. At the same time the possibility that these hormones may be elaborated by stromal cells is a very real one.

In a previous article (2) it was shown by the author that the endometrium in postmenopausal women did not always show a simple atrophic pattern. Active hyperplasia or proliferation of the endometrium was observed in just over 2.5 per cent of the cases. Moreover, Mack (3) found a slight estrogen effect in 27.6 per cent of asymptomatic postmenopausal women, and in a further 2.3 per cent there was a moderate estrogen effect.

The results show that measurable amounts of estrogen are excreted by women after the cessation of menstruation at the menopause. The amounts excreted vary greatly in different individuals and even from day to day in the same person.

No cyclic variation was observed over a period of six to eight weeks. This is in marked contrast to the cyclic variation noted by Brown during the menstrual cycle of women in the reproductive phase of life. This is not unexpected, as these variations are related to cyclic changes in the ovaries. It seems as though estrogen production in the younger woman is related to the growth of the Graafian follicle and then to the development of the corpus luteum. In the postmenopausal woman, in whom such changes are no longer taking place, it is probable that the estrogen is of different origin.

It has been suggested that the undifferentiated ovarian stroma of the cortex is capable of producing estrogen, but it seems doubtful if indeed the estrogen is being produced in the ovary. Even after bilateral oophorectomy the postmenopausal woman continues to produce quantities of estrogen similar to those found before operation or in the normal postmenopausal women. It may be that the suprarenal is the source of this estrogen found in elderly women. Moreover, it is known that estrogens in comparable amounts are found in the urine of adult males.

It is not unnatural to assume that the metabolic pathways and even the

chemical structure of the extra-ovarian estrogen may be different from those of ovarian hormones. There was nothing in the findings to suggest that estradiol-17β is the primary hormone, as Brown suggested was the case in the menstruating woman. The high level of estriol—which is the outstanding feature of this investigation—is not in agreement with his suggestion that estriol may be developed directly from the corpus luteum as well as from the metabolism of estradiol-17β.

There did not seem to be a constant relationship between the age of the patient or the length of time after the menopause and the amount of estrogen excreted. Thus fifteen to twenty years after the cessation of menstruation some patients produced equal or greater amounts than others only three to five years after the menopause.

The amount of estrogen excreted did not seem to vary according to the endometrial pattern. As was to be expected, the findings were approximately the same whether the cases were those in which no endometrium was obtained, or those in which the endometrium showed simple or cystic atrophy, or a senile polyp. The variations in individual cases and even in the same patient from day to day were considerable and this makes it difficult to assess the importance of the findings in the few cases in which cystic glandular hyperplasia was found. In these instances the levels of estrogen were high but they did not exceed the highest levels noted in cases in which the endometrium showed atrophic changes.

It must be emphasized that other estrogens known to occur in human urine are not estimated by Brown's method. These include 16-epi-estriol (7) and 16-x-hydroxyestrone (8). I have observed that when stilbestrol is given to a postmenopausal woman in sufficient quantity to produce vaginal cornification and endometrial hyperplasia there is no increase in the estradiol, estrone and estriol levels in the urine, whereas when estradiol is administered all three fractions are quickly increased until several hundred micrograms are excreted daily.

It is important to realize that the level of estrogen metabolites in the urine may furnish a very inadequate idea of the level of estrogen production and metabolism. The relationship need not be a direct one, and it may be that low levels of some of the components indicate a high degree of estrogen metabolism. Moreover, although estradiol, estrone and estriol represent the common pathway of metabolism, there may be other pathways, particularly if the estrogen is extra-ovarian in origin. This problem requires investigation.

SUMMARY

1. The quantity of estradiol, estrone and estriol in the urine of the normal postmenopausal woman is comparable to the amount excreted by women in the resting phase of the menstrual cycle.

2. There is no cyclic variation in the excretion of estrogen metabolites.

3. The quantity of estrogen excreted bears no direct relationship to the histologic pattern of the endometrium.

4. The postmenopausal woman produces comparable amounts of estrogen even after bilateral oophorectomy. This amount of estrogen is also found in the urine of the adult man.

Acknowledgments

I should like to thank Dr. A. D. T. Govan for his help in the preparation of this paper and Mr. K. Howells for his technical assistance in carrying out the estimation of estrogen.

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THE CHRONOLOGY OF EVENTS IN THE DEVELOPMENT OF SUBACUTE THYROIDITIS, STUDIED BY RADIOACTIVE IODINE

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THE clinical picture of subacute thyroiditis was described in 1904 by De Quervain (1). Since then, and especially in the last ten to fifteen years, there has been an increasing number of reports of this disease in the medical literature, with histologic studies and clinical observations (2–4). However, most of the problems of subacute thyroiditis have remained unsolved; its etiology is still unknown and the therapeutic approach is empiric.

Lately, radioactive iodine (I^{131}) has proved to be a useful tool in the investigation of this disease. Attention has been drawn (5–9) to the fact that the thyroidal uptake of I^{131} in subacute thyroiditis is low despite a clinical picture frequently presenting numerous signs of hyperthyroidism, often including high levels of serum protein-bound iodine.

CLINICAL MATERIAL AND METHODS

Using these observations as a basis, we studied 10 patients over a prolonged period of time. They were subjected to repeated I^{131} tests (10), the first being performed between the tenth and sixtieth day following the appearance of first symptoms. The tests were repeated every fifteen to thirty days during the first two months of illness, and then at intervals of two to four months.

During the period of observation the patients received no treatment.

The serum level of protein-bound iodine (PBI) and the erythrocyte sedimentation rate were determined concurrently. Occasionally the basal metabolic rate and serum cholesterol level were also determined. In Table 1 are listed the average values for the laboratory findings in the 10 cases of subacute thyroiditis.

In 1 case we repeated the experience of Robbins *et al.* (9); that is during the first stage of the disease the thyroidal uptake of I^{131} was increased by injecting thyroid-stimulating hormone (TSH) (Fig. 1). This is additional though incomplete evidence that TSH production is low during this stage.

Received December 5, 1956.

TABLE 1. LABORATORY FINDINGS (AVERAGE VALUES) IN 10 CASES OF SUBACUTE THYROIDITIS

Time after onset of the subacute thyroiditis	Thyroidal I^{131} uptake (% dose) at			Urinary I^{131} (% dose) at		Serum PBI (μg./100 ml.)	Erythrocyte sed. rate (mm./hr.)	BMR (%)	Serum tot. cholesterol (mg./100 ml.)
	2 hrs.	24 hrs.	48 hrs.	24 hrs.	48 hrs.				
Up to 1 mo.	3.1	4.1	3.9	60.0	69.3	12.3	96/112	+39	204
Up to 2 mos.	3.0	3.4	3.5	62.6	72.0	10.4	84/104	+35	210
Up to 3 mos.									
Group a	6.1	12.8	11.5	57.0	64.0	5.6	70/106	+ 6	243
Group b	11.3	28.5	24.2	51.5	57.8	7.8	76/98	+ 8	209
Group c	21.7	43.1	40.8	36.0	38.0	7.8	98/99	+ 5	206
Up to 4 mos.	16.7	42.0	40.4	33.4	38.0	9.9	59/74	—	215
Up to 5 mos.	17.2	40.4	38.5	38.0	41.2	8.9	28/39	—	209
From 6 to 12 mos.	12.3	28.7	28.7	45.7	49.0	7.8	18/28	+ 9	218
Our results in normal subjects	*10.0*	*30.0*	*29.2*	*45.0*	*48.0*	*4.0–8.0*	—	—	*150–250*

We were also interested in determining whether the changes in the results of the I^{131} tests were limited to the area of inflammation, or whether the entire thyroid gland reacted uniformly.

This question was investigated in 8 patients. The thyroidal uptake was

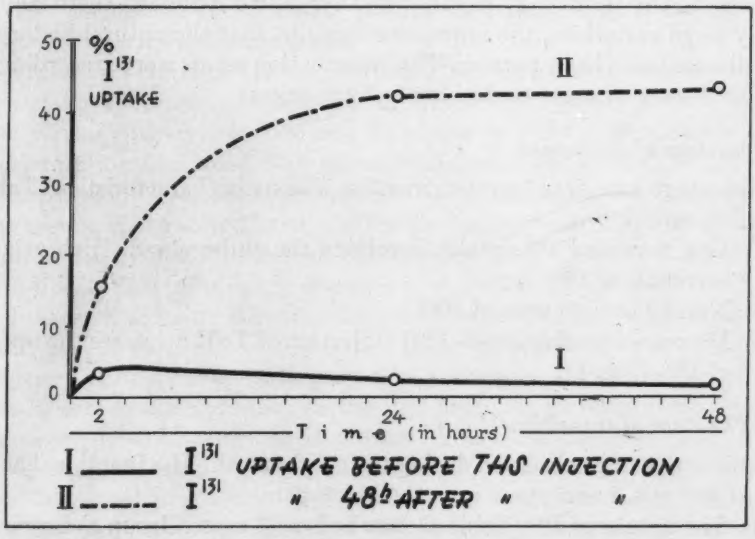

FIGURE 1

measured with the directional counter, so that differences between the inflamed area (clinically distinguished as a nodule) and other parts of the thyroid gland could be detected, should they exist. Generally speaking, there was uniformity in the uptake of the entire gland, although in a few instances the inflamed area temporarily absorbed less I^{131}. The results are listed in Table 2.

TABLE 2. MEAN VALUES (8 CASES) OF I^{131} UPTAKE OF INFLAMED THYROID GLAND MEASURED WITH DIRECTIONAL COUNTER TWENTY-FOUR HOURS AFTER INTAKE OF I^{131}

Area of thyroid examined	Days after onset of the disease					
	0–30	31–60	61–90	91–120	121–150	151
	Mean thyroidal uptake (% dose)					
Clinically inflamed area	0.7	2.0	22.5	31.0	34.6	27.0
Other parts of the thyroid	1.0	1.8	28.0	35.0	38.0	29.0

RESULTS

The results of the tests with radioactive iodine permit certain conclusions as to the chronology of subacute thyroiditis. Although there may be fairly large variations, the impression remains that the natural history of the disease has a basic pattern. This information seems worth recording.

The disease appears to develop in four stages:

I. *The stage of depression*

This stage lasts for about two months. The main characteristics (Tables 1 and 2) are:

1) Low thyroidal I^{131} uptake, involving the entire gland. High urinary excretion of I^{131}.
2) Normal or high level of PBI.
3) Decreased production of TSH (injection of TSH increases the uptake of I^{131}) (Fig. 1).

II. *The stage of transition*

This is the stage observed during the third month. The functional activity of the gland undergoes a gradual change:

1) The uptake of I^{131} (Table 1) may be low (2 cases, Group a) normal (4

cases, Group b), or high (4 cases, Group c), especially at the end of the month. Excretion of I^{131} changes from high to normal or low.

2) Serum PBI concentration approaches normal values.

III. *The stage of compensation*

This stage begins at the end of the third month and lasts for about four weeks:

1) The uptake of I^{131} increases slightly and may often reach elevated levels. Urinary excretion of I^{131} decreases.
2) Serum PBI values fall, usually to a lower level than previously, but may occasionally remain slightly high.
3) Production of TSH apparently takes the opposite turn. It is increased at the beginning and returns to normal at the end of the period.

IV. *The stage of remission*

After the stage of compensation the values for I^{131} uptake, I^{131} excretion, and serum PBI concentration gradually reach normal levels.

In the sixth to seventh month, results of all tests were normal in all our cases. In a certain percentage of the cases described in the literature the illness behaved differently, culminating in either permanent hypothyroidism (8) or hyperthyroidism (11).

DISCUSSION

The correlation of histologic studies with these results reveals what appears to be a valid explanation.

Fraser and Harrison (12), who studied the storage of thyroid hormone in the gland, found that the amount of hormone stored is sufficient to keep the patient euthyroid for two months even if no additional hormone is produced during this time. This two-month period corresponds to the stage of depression in subacute thyroiditis. The inflammatory infiltrate induces the release of the stored hormone into the bloodstream, thus increasing the concentration of PBI. The high PBI levels depress the production of TSH, and this in turn induces the decrease of thyroidal I^{131} uptake.

Inasmuch as under these conditions the release of thyroid hormone into the blood stream ensues, not as the result of pituitary activity but of a mechanical or inflammatory process in the gland, the depression of TSH production has no influence on the PBI level, which remains high as long as stored thyroid hormone is present. Following the utilization of this stock, the PBI level starts to fall and TSH production starts to increase. The increased production of TSH induces an increased activity of the thyroid gland and subsequently a compensatory increase of I^{131} uptake.

TABLE 3. CHRONOLOGY OF EVENTS IN SUBACUTE THYROIDITIS

Stage of disease	Time after onset of disease (mos.)	Laboratory Findings					
		Thyroidal I^{131} uptake	Urinary I^{131} excretion	Serum PBI	BMR	Erythrocyte sed. rate	Serum cholesterol level
I. Depression	1–2	Low	Elevated	Elevated, or upper limit of normal	Elevated or normal	Accelerated	Normal
II. Transition	3	Low, normal or elevated	Elevated, normal or low	Low, normal or elevated	Elevated or normal	Accelerated	Normal
III. Compensation	4–5	Elevated	Low	Elevated in a few; normal in most	Normal	Slightly accelerated	Normal
IV. Remission	5–12	Returning to normal	Returning to normal	Normal	Normal	Slightly accelerated or normal	Normal

During the last stage of the disease the production of both TSH and thyroxine finally reach their normal state of labile equilibrium.

By using these facts as a basis, it is possible to outline the chronology of events in the development of subactute thyroiditis (Table 3).

SUMMARY

Radioactive iodine appears to be a useful tool in the investigation of subacute thyroiditis.

Ten patients with subacute thyroiditis were studied in detail. The findings indicate that the disease develops in four functional stages.

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THE ASSOCIATION OF PERIODIC PARALYSIS AND HYPERTHYROIDISM IN JAPAN

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ALTHOUGH periodic paralysis is a rare disorder, its association with hyperthyroidism has been reported by several investigators (1–15). In reviewing the literature, it was found that only about 30 such cases have been reported from the United States and Europe, whereas more than 70 cases have been reported from Japan. Possibly the association of these two disorders is less rare in Japan. As the Japanese reports were all concerned with relatively small numbers of patients with hyperthyroidism, the incidence of the association of these two disorders in Japan could not be estimated. In order to obtain a fairly good estimate, the incidence of periodic paralysis among 6,333 cases of hyperthyroidism operated upon in three thyroid hospitals in Japan was studied. These hospitals were located in different parts of country—Noguchi Hospital in Beppu, Kyushu (southern part of Japan), Kuma Hospital in Kobe (central part of Japan) and Ito Hospital in Tokyo (eastern part of Japan), so the study provided data on a cross section of Japanese patient populations.

METHODS

A survey was made of the hospital records of patients with hyperthyroidism operated on during the following periods: between 1937 and 1956 in Noguchi Hospital, between 1941 and 1956 in Kuma Hospital, and between 1950 and 1956 in Ito Hospital. The diagnosis of hyperthyroidism was based upon the clinical findings and basal metabolic rate and was confirmed by the effect of treatment. In order to exclude uncertainty in the diagnosis as far as possible, ambulatory patients were not included; only those hospitalized and operated upon were studied. In about 50 per cent of the cases the diagnosis of periodic paralysis depended upon the history of the patient. In these instances, however, only patients with attacks of flaccid paralysis of the extremities were included, and special care was taken to ex-

Received March 29, 1957.

TABLE 1. INCIDENCE OF PERIODIC PARALYSIS ASSOCIATED WITH HYPERTHYROIDISM

	Number of cases of hyperthyroidism	Number of cases of periodic paralysis	Incidence of periodic paralysis (%)
Noguchi Hospital	2,852	39	1.4
Kuma Hospital	2,050	61	3.0
Ito Hospital	1,431	19	1.3
Total	6,333	119	1.9

clude patients with paralysis due to weakness of the muscles—a condition occasionally observed in cases of hyperthyroidism.

RESULTS

Incidence of periodic paralysis associated with hyperthyroidism. As shown in Table 1, periodic paralysis occurred in 119 of 6,333 cases of hyperthyroidism, an incidence of 1.9 per cent.

Relation to sex. There were 99 cases of periodic paralysis among 1,214 cases of hyperthyroidism in males, and 20 cases of periodic paralysis among 5,119 cases of hyperthyroidism in females (Table 2). The incidence

TABLE 2. INCIDENCE OF PERIODIC PARALYSIS IN HYPERTHYROIDISM, ACCORDING TO SEX

	Number of cases of hyperthyroidism	Number of cases of periodic paralysis	Incidence of periodic paralysis (%)
Male patients			
Noguchi Hospital	604	30	5.0
Kuma Hospital	385	50	13.0
Ito Hospital	225	19	8.4
Total	1,214	99	8.2
Female patients			
Noguchi Hospital	2,248	9	0.4
Kuma Hospital	1,665	11	0.7
Ito Hospital	1,206	0	0.0
Total	5,119	20	0.4

TABLE 3. FREQUENCY OF ATTACKS OF PERIODIC PARALYSIS

	More than one every 2 weeks	Once every 1–2 months	Once every 6–12 months
Noguchi Hospital	11	5	12
Kuma Hospital	27	8	28
Ito Hospital	5	8	6
Total	43	21	46

of the association was 8.2 per cent for male patients and 0.4 per cent for female patients.

Influence of heredity. A family history of periodic paralysis was noted in only 1 of the 119 subjects.

Frequency of attacks. The frequency of attacks of periodic paralysis is shown in Table 3.

Age of patient at onset of periodic paralysis. Table 4 shows the ages of the patients at the onset of periodic paralysis. The onset was most common in the decades 20–29 and 30–39.

Relationship between the onset of periodic paralysis and the onset of hyperthyroidism. This is shown in Table 5. The onset of hyperthyroidism was estimated from the time of the appearance of clinical symptoms. The onset of attacks of periodic paralysis coincided with, or followed the onset of hyperthyroidism in 73 per cent of the cases.

Remission of periodic paralysis after effective treatment of hyperthyroidism by subtotal thyroidectomy. Letters were sent to all patients, and 82 replied. Of these, 17 patients in Noguchi Hospital, 44 patients in Kuma Hospital and 14 patients in Ito Hospital had been euthyroid since thyroidectomy. The period of observation ranged from one year to nineteen years. In most cases the attacks of periodic paralysis had subsided after hyperthyroidism was relieved, as shown in Table 6.

TABLE 4. AGE OF PATIENT AT ONSET OF PERIODIC PARALYSIS

	Age (yrs.)				
	below 19	20–29	30–39	40–49	over 50
Noguchi Hospital	2	17	16	2	2
Kuma Hospital	4	24	26	5	0
Ito Hospital	3	11	2	1	0
Total	9	52	44	8	2

TABLE 5. RELATIONSHIP BETWEEN THE ONSET OF PERIODIC PARALYSIS AND THE ONSET OF HYPERTHYROIDISM (BASED ON THE RECOLLECTION OF THE PATIENT)

	Hyperthyroidism first	At approximately the same time	Periodic paralysis first	Not known*
Noguchi Hospital	10	11	10	8
Kuma Hospital	31	19	9	2
Ito Hospital	10	6	1	2
Total	51 (43%)	36 (30%)	20 (17%)	12 (10%)

* Patient could not recall accurately.

DISCUSSION

In this study, periodic paralysis was observed in 1.9 per cent of patients with hyperthyroidism—a fairly high proportion compared with the incidence of periodic paralysis in the general population. Several mild cases of hyperthyroidism were not included in the study because the patients were not hospitalized and operated upon; if they had been included, the incidence of periodic paralysis in this disease might have been lower. Even with this consideration, the association of the two disorders appears to be more common in Japan than in Europe and the United States, if one can judge from the number of reports in the literature. The cause for this is not clear, but the factors to be considered include racial and dietary differences, *e.g.*, the high carbohydrate content of the Japanese diet.

The data show that the two diseases are much more likely to occur together in the male than in the female, in a ratio of 20.5 to 1. This relationship is different from that in uncomplicated periodic paralysis (16), in which the ratio is 3:1. This difference should receive special attention.

It has been recognized that in patients with uncomplicated periodic par-

TABLE 6. PERSISTENCE OF ATTACKS OF PERIODIC PARALYSIS AFTER EFFECTIVE TREATMENT OF HYPERTHYROIDISM

	Number of cases followed	Number with persistent periodic paralysis
Noguchi Hospital	17	0
Kuma Hospital	44	3
Ito Hospital	14	0
Total	75	3

alysis the hereditary occurrence of the disease is high, but in cases associated with hyperthyroidism there is usually no family history of paralysis. This observation was confirmed in the present study; a family history of the disease was noted only in 1 of the 119 patients with periodic paralysis.

Uncomplicated periodic paralysis usually develops in the first two decades of life, especially during adolescence, and it is said that onset later than the third decade is rare. In our study, the onset of periodic paralysis was most common in the age groups 20–29 and 30–39; 2 patients were over 50 at the time of onset. This is definitely different from the age distribution for uncomplicated periodic paralysis.

In 73 per cent of the present series, the initial attack of periodic paralysis occurred after, or at the time of the appearance of thyrotoxic symptoms. In cases in which attacks of periodic paralysis preceded the onset of hyperthyroidism, there is the possibility that some of the patients might have been in a state of latent hyperthyroidism.

The absence of family history, the older age of the patient at the onset of paralytic attacks, the exceedingly high occurrence in males compared to females, and the subsidence of paralytic attacks after effective treatment for hyperthyroidism in most cases, suggest that the periodic paralysis associated with hyperthyroidism may be a separate disorder from uncomplicated periodic paralysis. However, the neuromuscular symptoms are in no way distinguishable from those of uncomplicated periodic paralysis. As it has been shown that attacks of paralysis can be precipitated by the administration of thyroid hormone in uncomplicated periodic paralysis (3), it is conceivable that in some patients pre-existing latent periodic paralysis becomes manifest upon the development of hyperthyroidism. In some of the cases in which the onset of periodic paralysis was preceded by the onset of hyperthyroidism, the association might have been by chance.

Little is known about the relationship between periodic paralysis and hyperthyroidism. It has been known that attacks of periodic paralysis can be precipitated by the ingestion of a large amount of carbohydrate and by the injection of epinephrine. As excessive amounts of thyroid hormone affect carbohydrate metabolism and increase the sensitivity of some tissues to epinephrine, it is conceivable that the thyroid hormone precipitates attacks through these mechanisms.

SUMMARY

1. Periodic paralysis was observed in 119 of 6,333 patients with hyperthyroidism operated on in three thyroid hospitals in Japan. On this basis, the incidence of periodic paralysis in hyperthyroidism was 1.9 per cent.

2. Among 1,214 male patients with hyperthyroidism, periodic paralysis was observed in 99, an incidence of 8.2 per cent; and among 4,847 female patients it was observed in 20, an incidence of 0.4 per cent.

3. A family history of periodic paralysis was noted in only 1 of the 119 cases.

4. The age of the patient at the onset of paralytic attacks was most frequently in the groups 20–29 and 30–39 years. This is different from the age at onset of uncomplicated periodic paralysis.

5. In the majority of cases the onset of attacks of periodic paralysis approximately coincided with, or followed the onset of hyperthyroidism.

6. The attacks of paralysis usually disappeared after effective treatment for hyperthyroidism.

Acknowledgment

We wish to express our thanks to Dr. Neil J. Elgee for correction of English in the manuscript submitted.

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CORTICOSTEROID RESPONSE TO SURGERY: EFFECT OF TESTOSTERONE

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THE trauma of a surgical operation is quickly followed by a release of corticotropin from the anterior pituitary, which in its turn stimulates the adrenal cortex to synthesize and secrete 17-hydroxycorticosteroids (17-OHCS). The rise in the level of free and conjugated plasma 17-OHCS lasts for a few days (1) and reflects a balance between the rate of secretion of free 17-OHCS, and their conjugation and elimination by metabolism or urinary excretion. It has been amply demonstrated that although there is some loose relationship between the amount of surgical trauma, the rise in plasma 17-OHCS levels and the total urinary corticosteroid excretion, many other factors are probably involved, such as the age of the patient or the type of disease (2). Even when these known influences are taken into account it is difficult to explain the wide differences in plasma levels and urinary 17-OHCS excretion among a fairly homologous group of patients following a standard operation such as partial gastrectomy (2). It is therefore of interest to find other causes for these variations. Gemzell and Notter (3) observed that when androgens were administered for some days before operation the expected rise in the plasma level of free 17-OHCS failed to occur. In patients not receiving androgens, the plasma level increased from the preoperative average value of 5.6 μg. per 100 ml. to 31.4 μg. per 100 ml. at one hour, and 29.5 μg. per 100 ml. at twenty-four hours after operation; whereas in 5 patients receiving testosterone propionate for four to six days the plasma levels were no higher than 7.0 μg. per 100 ml.

Flear and Clarke (4) suggested that loss of blood and an inadequate circulating blood volume are major factors in the etiology of post-traumatic metabolic changes. Their studies were restricted to the metabolism of water and electrolytes after trauma and did not include steroid estimations.

The present investigations were undertaken to study (a) the relationship between androgen therapy, postoperative urinary 17-OHCS excretion and cumulative electrolyte balance, and (b) the effects of oligemia, and its correction, on urinary total 17-OHCS excretion.

Received March 3, 1957.

* Supported by Medical Research Council Grant.

† Supported by the Board of Governors of the United Sheffield Hospitals.

PLAN OF STUDY AND TECHNICAL METHODS

These investigations were carried out on 14 adult male patients (41 to 66 years old) who were submitted to partial gastrectomy under general anesthesia (pentobarbital sodium intravenously; nitrous oxide and oxygen; curare) for chronic peptic ulceration. Operative and anesthetic conditions were standardized as far as possible. For a few days before operation and for five to seven days postoperatively each patient was maintained on a diet of milk with varying electrolyte supplements and the urine was collected in 24-hour quantities. Aliquots of the milk and urine were analyzed for sodium, potassium, chloride and nitrogen; in addition, the urinary excretion of total 17-OHCS was estimated.

The chemical methods used were: for sodium and potassium, flame photometry; for chloride, potentiometric titration (5); for nitrogen, the micro-Kjeldahl method; and for total 17-OHCS, Norymberski's method (6).

Intravenous infusions were not given before, during or after operation except in the patients of Group 3, who received blood.

There were no complications or sustained pyrexia in the convalescence of these patients. Stools and sweat were not estimated.

The 14 patients were divided into 3 groups according to therapy: In Group 1 (no treatment) and in Group 2 (intramuscular testosterone before and after operation) electrolyte balance and steroid excretion were studied. In Group 3 (blood intravenously during operation, but no testosterone) electrolyte balance studies were not performed.

RESULTS

Group 1. This consisted of 4 patients (aged 53 to 66 years) who did not receive any supplementary blood or testosterone propionate. The final cumulative balance studies (Table 1) for five to seven days postoperatively revealed an average sodium retention of +30 mEq. (range, −30 to +96);

TABLE 1. *Group 1:* PATIENTS WHO DID NOT RECEIVE SUPPLEMENTARY BLOOD OR TESTOSTERONE PROPIONATE

The estimations represent the cumulate (for five to seven postoperative days) balance of sodium (Na), potassium (K) and chloride (Cl) calculated in mEq., and nitrogen (N) in Gm. The 17-hydroxycorticosteroid (17-OHCS) values represent (in mg./24 hrs.) the mean of the urinary excretion for the first four postoperative days.

Patient No.	Age (yrs.)	Na	K	Cl	N	17-OHCS
1	55	+95	−178	+141	−48.5	19.6
2	53	− 6	− 13	+ 91	−17.5	26.8
3	66	−30	+ 55	+ 71	− 0.9	21.2
4	62	+96	+127	+127	−11.1	40.6
Mean		*+36*	*− 2*	*+107*	*−19.5*	*27.1*
Davies *et al.* (7): 95% range		−189 to +389	−155 to +139	−236 to +526	−30 to −100	
Mean		+105	− 8	+145	−65.6	

potassium, −2 mEq. (range, −178 to +127); chloride, +107 mEq. (range, +71 to +141); and nitrogen, −19.5 Gm. (range, −0.9 to −48.5). The mean steroid excretion of these patients for the first four postoperative days was 27.1 mg. per twenty-four hours (range, 19.6 to 40.6). The maximal 24-hour excretion was on the second or third day and the duration of the elevated excretion above an arbitrary upper limit (16.2 mg.) of the normal range was three to seven days (2).

Group 2. This consisted of 6 patients (aged 46 to 65 years) who received 50 mg. of testosterone propionate intramuscularly twice daily (100 mg. per day) for four days prior to, and four days after operation. The cumulative balance figures are listed in Table 2. The average postoperative retention of sodium was +172 mEq. (range, +123 to +266); potassium, +5 mEq. (range, −93 to +143); chloride, 206 mEq. (range, +136 to +296); and nitrogen, −36.5 Gm. (range, −9.8 to −53.2). The excretion of total 17-OHCS expressed as the mean of values for the first four postoperative days was 26.9 mg. per twenty-four hours (range, 13.2 to 42.2). The maximal daily postoperative excretion was in the second or third 24-hour period and the duration of the increased steroid response beyond the upper limit (16.2 mg.) of the normal range varied from two to seven days.

TABLE 2. *Group 2:* PATIENTS WHO RECEIVED 100 MG. OF TESTOSTERONE PROPIONATE DAILY FOR FOUR DAYS PRIOR TO, AND FOUR DAYS AFTER OPERATION

The estimations represent the cumulate (for five to seven postoperative days) balance of sodium (Na), potassium (K) and chloride (Cl) calculated in mEq., and nitrogen (N) in Gm. The 17-hydroxycorticosteroid (17-OHCS) values represent (in mg./24 hrs.) the mean of the urinary excretion for the first four postoperative days.

Patient No.	Age (yrs.)	Na	K	Cl	N	17-OHCS
5	52	+266	− 93	+296	−48.8	13.2
6	50	+152	− 40	+140	−53.2	18.2
7	46	+179	+147	+233	−18.3	22.8
8	50	+123	− 60	+136	−42.4	42.2
9	57	+147	− 66	+208	−46.7	40.2
10	65	+166	+143	+225	− 9.8	24.9
Mean		*+172*	*+ 5*	*+206*	*−36.5*	*26.9*

Group 3. These 4 patients (Nos. 11–14, aged 41 to 60 years) received an intravenous infusion of 1 to 1½ liters of blood during the operative period. The transfusion more than covered the estimated blood loss of 250–500 ml. and was sufficient in 3 of the 4 patients to raise the systolic blood pres-

sure by 20–30 mm. Hg above the preoperative level. The mean daily steroid excretion for the first four postoperative days was 21.3 mg. per twenty-four hours—Patient 11, 27.5 mg.; Patient 12, 19.1 mg.; Patient 13, 15.7 mg.; and Patient 14, 23.0 mg. The maximal excretion was on the second day in all cases and the duration of the raised excretion was two to seven days.

DISCUSSION

The metabolic changes which follow partial gastrectomy have been extensively studied in relation to electrolyte balance and steroid excretion under conditions essentially similar to those in the present investigations. In previously reported experiments by one of us (7) the average postoperative retention of sodium was 105 mEq. (95 per cent range, −189 to +389); potassium, −8 mEq. (95 per cent range, −155 to +139); chloride, 145 mEq. (95 per cent range, −236 to +526); and nitrogen, −65.6 Gm. (95 per cent range, −30 to −100). In another series (2) of 19 patients undergoing partial gastrectomy for chronic peptic ulceration the mean 24-hour output of total 17-OHCS for the first four postoperative days was 27.6 mg. (range, 15.7 to 45.0), with the maximal output usually on the second day. The mean four-day figure is used as a convenient comparison between cases, as the maximal output may vary from the first to the third day (2). The electrolyte balance in Group 1 reported in the present paper exhibited the same trend and proportion as in the foregoing cases, that is, a moderate retention of sodium and chloride and virtually total recovery from the potassium diuresis of the early postoperative days. The nitrogen loss was considerably less in the present series. The average daily steroid excretion for the first four postoperative days, its duration, and the maximal 24-hour output were comparable to those observed in the larger series of Reece *et al.* (2).

In Group 2—patients who received testosterone—the electrolyte and nitrogen trends were essentially similar to those in Group 1; the greater nitrogen loss in Group 2 failed to confirm the supposed anabolic action of androgens. Similarly, the steroid excretion and electrolyte balance remained at much the same levels as in Group 1. It is believed that testosterone per se and its metabolic degradation products do not influence the urinary excretion of 17-OHCS. Appleby *et al.* (6) found that the addition of dehydroepiandrosterone (50 μg. per ml.) to several urines taken at random did not cause any significant increase of the determined 17-OHCS.

In both Groups 1 and 2 there was no observed relationship between steroid excretion and the retention or otherwise of the electrolytes. This supports a similar conclusion drawn from a study of patients with electrolyte retention following pyloric stenosis (8).

In Group 3 a deliberate effort was made to prevent oligemia or reduction

in circulating blood volume; in fact these patients were overtransfused as indicated by a rise in blood pressure. The mean steroid output remained, however, little different from that in the preceding groups. This evidence suggests that neither androgen therapy nor blood replacement grossly alters the steroid response to the operative trauma of partial gastrectomy and does not suppress the expected increased urinary steroid excretion. These findings do not necessarily conflict with those of Gemzell and Notter (3), whose studies were limited to the plasma levels of free 17-OHCS, as it is known that the relationship of blood steroid values to the urinary excretion of total steroids is not predictable (9). It is unlikely that androgens suppress either the release of corticotropin by the pituitary or the synthesis of steroids by the adrenal, as the total urinary output remained unchanged in this series; nor is it probable that androgens influence steroid excretion by modifying the levels of nitrogen or electrolytes. It seems most probable that androgen therapy alters the rate at which 17-hydroxycorticosteroids pass from the plasma into the tissues or tissue spaces, or the rate at which free steroids are conjugated. Either variant would effectively reduce the plasma levels of free 17-OHCS without necessarily altering total urinary excretion. Further information concerning the modification of the proportions of free and conjugated plasma steroids under the influence of androgen therapy is therefore needed. It seems also very unlikely that the moderate oligemia sustained by an uncomplicated major abdominal operation significantly alters steroid excretion, although severe operative hemorrhage may be a factor, as is pyrexia, in prolonging the response.

SUMMARY

The urinary excretion of 17-hydroxycorticosteroids has been estimated in a group of 14 patients undergoing partial gastrectomy.

The mean 17-hydroxycorticosteroid excretion over the first four postoperative days was not influenced by either intramuscular testosterone therapy or intravenous over-replacement of blood loss, nor could any relationship be found between these two types of therapy and the retention or otherwise of sodium, potassium and chloride.

It is suggested that these findings can be reconciled with the reputed suppression of free plasma 17-hydroxycorticosteroid levels by postulating that the rate of conjugation or passage out of the plasma of these compounds is modified by testosterone therapy.

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EXOPHTHALMOS AND LOCALIZED PRETIBIAL MYXEDEMA IN A EUTHYROID PATIENT: STUDIES WITH TRIIODOTHYRONINE*

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RARELY, patients exhibit eye signs of Graves' disease without evidence of thyroidal overactivity. These cases may represent a variant of Graves' disease with eye signs manifest prior to hyperthyroidism. Occasionally, however, hyperthyroidism does not develop.

A series of such patients has recently been studied by Werner (1), who found that they exhibited the abnormal response to administration of triiodothyronine and thyrotropin characteristic of patients with active thyrotoxicosis, in spite of the fact that by ordinary clinical and laboratory criteria they were euthyroid at the time of study.

Localized pretibial myxedema, also a relatively rare sign, characteristically appears during active hyperthyroidism or after treatment has been initiated (2). To my knowledge, its occurrence without antecedent hyperthyroidism has been reported only once (3).

The present patient had both marked exophthalmos and localized myxedema without hyperthyroidism. In studies of the effect of triiodothyronine on the thyroidal secretion rate, there was an abnormal response. The concentration of labelled triiodothyronine in the skin of the localized myxedematous area was found to be the same as the concentration in the patient's normal skin.

CASE REPORT

A 61-year-old white housewife[1] entered the University of Oregon Hospital with the chief complaint of bulging of the eyes for approximately two years. She had first noticed protrusion of the right eye followed by swelling of the eyelid; approximately one week later the same process developed in the left eye. The condition had became progressive, with intermittent exacerbations and remissions until the time of admission. There had been some blurring of vision, especially when the eyes seemed more protuberant. There was no intolerance of heat or cold, change in the hair, diarrhea, tremor, palpitation or other symptoms of thyrotoxicosis, although she had been somewhat nervous and irritable with the onset of the ocular condition. Her appetite had been constant but she had

* Supported in part by Grant A-1447 from the National Institutes of Health. The triiodothyronine used in this study was generously supplied by Smith, Kline & French Laboratories.

[1] I am indebted to Dr. E. L. Gardner for allowing us to study this patient.

gained about 15 pounds in the preceding year. Her family history was of interest, in that one sister had had a goiter removed many years previously; it was not known whether this was a "toxic" goiter. At the same time the patient had been given "iodine drops," but she was unaware of any thyroid enlargement or symptoms of thyrotoxicosis then or since.

System review revealed nothing remarkable except for the condition of the lower extremities. For the previous ten years she had been bothered by swelling of the ankles. At first the swelling occurred sporadically, and was evident only in the evening; it involved the ankles and lower legs and would disappear overnight on bed rest. There was no change in the texture or color of the skin. Approximately six to nine months before entry the swelling became constant and was associated with a thickening of the skin, which at times became red and itchy. It was much worse when she was on her feet and always improved with bed rest. The thickening of the skin initially involved the area over the ankles, but by the time of admission had extended inferiorly to the dorsal surface of the feet, and superiorly to the upper third of the lower legs.

On physical examination her temperature was 98.8° F., blood pressure 150/80 mm. Hg, respirations 20, pulse 80, height 5 feet 6 inches (168 cm.), and weight 130 pounds (59 Kg.). She was a cooperative, somewhat anxious, fairly well nourished woman of the stated age. The skin was smooth and of normal temperature and the palms were slightly moist and cool. There was marked bilateral exophthalmos (measuring 31 mm. on each side) and fairly pronounced periorbital edema. There was definite widening of the palpebral fissure, with stare but no lid-lag. Extraocular movements were intact except for slight weakness of the right rectus muscle and subjective diplopia on extreme right lateral gaze. Visual field and funduscopic examinations yielded normal results. The thyroid gland was not palpable and no bruit was detected in the thyroid region. There was marked elevation as well as thickening of the skin over an area ranging from the dorsum of the foot to the mid-calf. This skin was very hard, dry and rough, and there was no pitting. There was a reddish-purple cast to the involved areas, which at times appeared slightly yellowish, translucent, and waxy. The soles of the feet and the toes were not involved. The remainder of the physical examination showed nothing remarkable, except for a palpable liver which extended 2 centimeters below the costal margin.

The results of routine urinalysis, blood count, and liver function tests were normal. Values for serum sodium and potassium, fasting blood glucose, and blood protein levels were also within normal limits. Thyroidal radioiodine uptake was 30.6 per cent in twenty-four hours, and the concentration of serum protein-bound iodine was 4.8 μg. per 100 ml. Upon biopsy of the affected skin of the lower leg the histologic picture was considered by the pathology department to be characteristic of myxedema.

EXPERIMENTAL STUDIES

The thyroidal secretion rate of this patient was studied as previously described (4); a dose of 300 microcuries of I^{131} was administered orally and twenty-four hours later daily counts over the thyroid gland with an externally placed scintillation counter were begun. The patient was given 30 mg. of methimazole every eight hours, beginning at the time of the initial thyroidal count, in order to block the reaccumulation in the thyroid gland of I^{131} released from the catabolism of endogenously labelled hormone. Thyroidal radioactivity was corrected for physical decay and plotted on semi-log paper (Fig. 1). Methimazole in this dosage may not completely

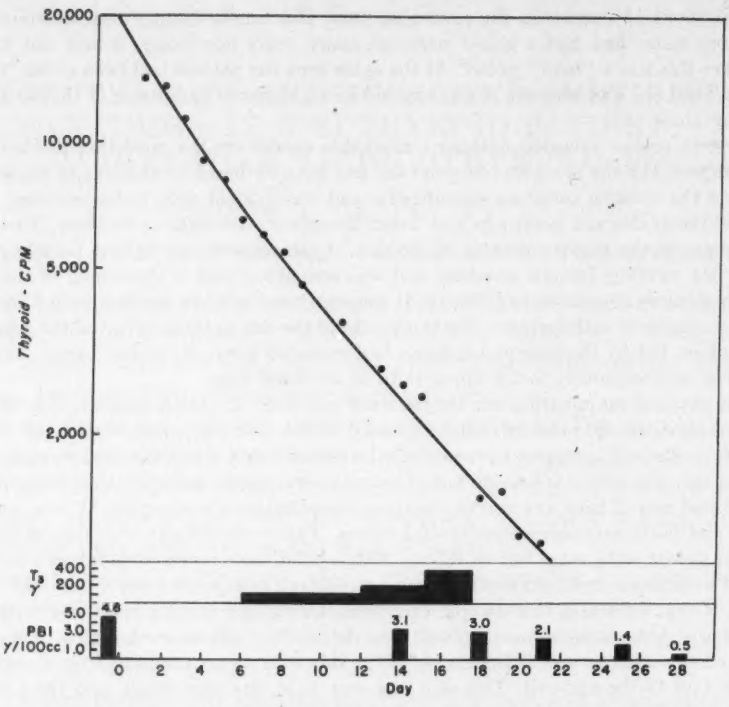

FIG. 1. Decrease in thyroidal radioactivity expressed in counts per minute corrected for physical decay. T_3 = triiodothyronine in micrograms administered orally per day. PBI = protein-bound iodine in micrograms per 100 ml. of serum.

block reaccumulation of iodine in all patients, but in most of them the block is fairly complete and the 24-hour thyroidal I^{131} uptake will be reduced to less than 5 per cent (5). Actually, the thyroidal loss measured by this technique is only that of I^{131}, but this probably is in large part a reflection of the loss of hormonal iodine. For this reason the term "thyroidal secretion rate" is used, even though it may not be strictly accurate.

After determination of the initial secretion rate, triiodothyronine was administered daily from the sixth through the seventeenth day, beginning with 100-μg. doses and increasing to 400 μg. The initial thyroidal secretion rate indicated a biologic half-life of four days. This was more rapid than that seen in any euthyroid patient previously studied in this laboratory. The average half-life in such euthyroid patients has been approximately thirty days, with a range of seven to one hundred and sixty-four days. This patient's secretion rate put her in a category with the most active group of thyrotoxic patients, in whom the average half-life has been approximately seven days.

TABLE 1. RADIOACTIVITY OF BIOPSY SPECIMENS OF SKIN FROM NORMAL AND FROM MYXEDEMATOUS AREAS OF LEG COMPARED WITH THAT OF SERUM, TWO TO THREE HOURS AFTER INTRAVENOUS ADMINISTRATION OF LABELLED TRIIODOTHYRONINE

Tissue	Weight (Gm.) of specimen	Radioactivity (counts/min.)	Radioactivity (cpm/Gm.)	Ratio tissue/serum radioactivity
Normal skin	0.238	498	2,095	0.201
Myxedematous skin	0.612	1,168	1,910	0.183
Serum	2.0	20,924	10,462	

Upon administration of triiodothyronine, the secretion rate was slightly but probably not significantly decreased to a half-life of five and a half days. There was no greater effect from 400 μg. of triiodothyronine daily than from 100 μg., although the patient exhibited definite evidence of hyperthyroidism while taking the larger doses (equivalent to 16 grains of desiccated thyroid daily). This was manifested by weight loss, tachycardia, tremor, nervousness, excessive sweating, and heat intolerance. All signs and symptoms of hyperthyroidism except the weight loss disappeared within forty-eight hours after discontinuing triiodothyronine.

Serum protein-bound iodine levels fell progressively and rapidly, especially toward the end of the period of methimazole administration. By the twenty-eighth day of treatment they had dropped from an initial level of 4.8 μg. per 100 ml. to 0.5 μg. This fall in the concentration of serum protein-bound iodine was more rapid than previously seen in any non-thyrotoxic patient. No clinical evidence of hypothyroidism had developed at the time the protein-bound iodine level was 0.5 μg. per 100 ml., but it was necessary to terminate methimazole therapy at that time because of the development of a generalized skin rash.

On the twenty-second day of study, a dose of 500 microcuries of labelled triiodothyronine[2] was injected intravenously and two to three hours later a section of skin from the myxedematous area over the ankle and a section of normal skin from the mid-thigh were removed. These tissues were weighed, fixed in formalin, and counted in a scintillation well counter. The concentration of radioactivity in these two tissues was compared to that of serum from blood taken at the same time as the biopsy specimens, after correcting for residual radioactivity in the serum due to the previous administration of I^{131}. The concentration in both normal and myxedematous skin was approximately 20 per cent of that in serum (Table 1).

[2] Obtained from Abbott Laboratories.

DISCUSSION

The abnormally rapid thyroidal secretion rate and the fact that it could not be significantly suppressed by triiodothyronine in this patient are consistent with previous results reported by Werner (1) of the failure of triiodothyronine to suppress radioiodine uptake in patients with exophthalmos without hyperthyroidism. In a small series of patients studied so far in this laboratory it has been found that in euthyroid subjects there is prompt suppression of thyroidal secretion following administration of a physiologic amount of triiodothyronine, whereas in thyrotoxic patients there is no such suppression even with doses up to 2,000 μg. of triiodothyronine daily.

The cause of the abnormal thyroidal activity in the present case is not apparent. It is obvious that turnover in the thyroid must have been very fast. The dramatic fall in the level of serum protein-bound iodine was much more rapid than any we have seen even in thyrotoxic patients and, when considered along with the rapid secretion rate, suggests a small pool of hormonal iodine in the thyroid. In all probability clinical thyrotoxicosis will eventually develop in this patient, but at the present time (more than twelve months after the initial admission) she is euthyroid.

Previous studies of the concentration of triiodothyronine in normal and myxedematous skin have not been found. In this patient, the concentration of labelled triiodothyronine in the skin was about 20 per cent of that in the serum. This proportion is roughly comparable to the skin/serum ratio of 0.5 in the mouse as reported by Gross (6). Our results would indicate that, whatever the cause of the localized myxedema, it is not related to a relative failure of triiodothyronine to enter the tissues of the skin.

SUMMARY

Studies have been made on the effect of triiodothyronine on the thyroidal secretion rate of I^{131} in a patient with exophthalmos and localized myxedema without hyperthyroidism. The thyroidal secretion rate was found to be much more rapid than that seen in other euthyroid patients and more rapid than the average for most thyrotoxic patients. It was not significantly suppressed by the oral administration of up to 400 μg. of triiodothyronine daily in spite of the production of toxic symptoms by this large dose. In addition, studies were made of the penetration of labelled triiodothyronine into the normal skin and into the skin of the localized myxedematous area. There was no significant difference between the concentrations in these two tissues.

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Letters to the Editor

ANALYSIS OF THE PHOSPHORUS REABSORPTION INDEX: THEORETICAL AND PRACTICAL IMPLICATIONS*

To the Editor:

The "phosphorus[1] reabsorption index" (PhRI)[2] was devised and first employed by Crawford *et al.* (1) and may be defined in terms of its physiologic significance as follows:

$$[1] \qquad \text{PhRI} = \frac{\text{TRPh}}{\text{GFPh}}$$

where TRPh = tubular reabsorption of phosphorus, and GFPh = glomerular filtration of phosphorus. In the studies of Crawford *et al.* and in our own experience and that of others (2, 3), determination of the index has proved valuable for the experimental and clinical study of abnormal kidney function with respect to phosphate excretion. The index is conventionally calculated as follows: GFPh (mg./min.) is the product of serum phosphorus concentration times glomerular filtration rate (GFR), which is in turn usually estimated, for this purpose, as the clearance of endogenous creatinine; and TRPh (mg./min.) is GFPh minus urinary phosphorus (mg./min.).

The fact that this conventional method of calculating the index is unnecessarily elaborate from the mathematical standpoint has already been noticed (3), but the identity of the conventional and simplified calculations has not been derived in general form nor have the theoretical and practical implications of this identity been explicitly set forth.

Of any substance present in the plasma in wholly filtrable form (as phosphorus normally is), it is evident that the extent of net renal tubular reabsorption (or secretion) is reflected by the deviation of the value for the

* Studies of the phosphorus reabsorption index in this clinic have been facilitated by the award of a Graduate Training Grant in Endocrinology by the National Institute of Arthritis and Metabolic Diseases and by research grant H-2533 from the National Heart Institute.

[1] "Phosphorus" means, throughout, inorganic phosphorus.

[2] PhRI, TRPh and GFPh are used instead of the customary abbreviations PRI, TRP and GFP, only to avoid confusion with the symbol P, which is used subsequently in the conventional manner to mean blood plasma.

renal clearance of that substance from the glomerular filtration rate. In the case of a substance not secreted by the renal tubule, the ratio of its clearance to glomerular filtration rate expresses the proportion of filtered material escaping reabsorption, and hence, making the assumption that phosphorus is not secreted by the tubule, we may write:

$$[2] \qquad \frac{TRPh}{GFPh} = 1 - \frac{C_{Ph}}{GFR}$$

where C_{PH} = renal clearance of phosphorus.

From [1] and [2],

$$[3] \qquad PhRI = 1 - \frac{C_{Ph}}{GFR} \fallingdotseq 1 - \frac{C_{Ph}}{C_{Cr}}$$

where C_{Cr} = the clearance of endogenous creatinine.

The index, then, is in common practice derived entirely from the ratio of phosphorus clearance to creatinine clearance. According to the standard procedure for carrying out the test, however, these clearances are determined simultaneously on one or more timed urine samples; and for the clearance of any two substances A and B so determined, *i.e.*, by estimating urinary excretion of both per unit time on one and the same urine sample, the ratio of the clearances must depend exclusively on the values for the concentrations of the substances in blood plasma and in urine; for

$$[4] \qquad C_A = \left(\frac{UV}{Pt}\right)_A \quad \text{and} \quad C_B = \left(\frac{UV}{Pt}\right)_B$$

by definition, where C_A = clearance of A; C_B = clearance of B; U and P = concentrations of A and B in urine and plasma respectively; and t = time. When the concentrations of A and B in urine are determined on the same urine sample, V and t are constants:

$$[5] \qquad \left(\frac{V}{t}\right)_A = \left(\frac{V}{t}\right)_B$$

and hence [4] reduces to:

$$[6] \qquad \frac{C_A}{C_B} = \frac{\left(\frac{U}{P}\right)_A}{\left(\frac{U}{P}\right)_B}$$

i.e., the ratio of the clearances of A and B is given by the ratio of the U/P ratios of the two substances. *A fortiori:*

$$[7] \qquad \frac{C_{Ph}}{C_{Cr}} = \frac{\left(\frac{U}{P}\right)_{Ph}}{\left(\frac{U}{P}\right)_{Cr}}$$

and hence from [3] and [7],

$$[8] \qquad PhRI = 1 - \frac{\left(\frac{U}{P}\right)_{Ph}}{\left(\frac{U}{P}\right)_{Cr}}.$$

For routine calculation, the transposed form of [8] is most convenient:

$$[9] \qquad PhRI = 1 - \frac{[Ph]_U[Cr]_P}{[Ph]_P[Cr]_U}.$$

Nordin and Fraser (4), while studying effects of intravenous infusions of calcium, utilized the ratio of phosphorus clearance to creatinine clearance (C_{PH}/C_{Cr}) to express effects upon the proportion of filtered phosphorus escaping reabsorption by the tubules, and observed that this index is not influenced by minor errors in the timing of urine collection. They were apparently unacquainted with the phosphorus reabsorption index previously derived by Crawford *et al.* and applied by them to study of the same function. Chambers *et al.* (3) presented specific calculations to show that $1-C_{Ph}/C_{Cr}$ is mathematically identical with PhRI, but they seem not to have grasped the implications of this fact. Respecting the use of $1-C_{Ph}/C_{Cr}$ instead of the redundant calculation of Crawford *et al.*, they state only: "Use of this shortened formula for TRP has distinct advantages . . . elimination of urine volume and time from the final calculation avoids errors caused by inexact collection, timing, or incomplete emptying of the bladder." This is incorrect; it is neither the elimination of V/t from the final calculation nor (what is the same thing) the use of the shortened formula which avoids these errors; both methods of calculation must result in the same final value since they are mathematically identical. The relatively low error of the ratio of any simultaneously determined clearances is inherent in the data, not in the mode of reckoning; and the appearance of V/t in the longer calculation of PhRI represents merely the intrusion and subsequent elimination of an extraneous datum.

It will be seen that the expression used by Nordin and Fraser—$(1-C)_{Ph}/C_{Cr}$—is preferable in strictness to the term PhRI (or % phosphorus reabsorption), since a ratio of simultaneous clearances is in fact what is determined, and since the validity of the datum is logically antecedent to and

independent of the inferred intrarenal events in terms of which it is interpreted.

The fact that V/t is irrelevant to the calculation of simultaneous clearance ratios has theoretical and practical implications of considerable moment. It explains the strikingly low variance of serial determinations of $1-C_{Ph}/C_{Cr}$ as compared with the estimation by conventional means of the renal clearance of any single substance, in which a major source of inaccuracy is the error of estimating V/t. General acceptance of the phosphorus reabsorption index, a test which in our opinion deserves widespread use, might be delayed should it appear that the notably narrow range of normal values (.88–.96 in our experience, provided fasted subjects whose dietary phosphorus has been restricted for several days are used) claimed for $1-C_{Ph}/C_{Cr}$ were based upon individual clearance data which could hardly yield a derived datum of such high precision.

The irrelevance of V/t to the calculation entails also the important practical consequence that the methodology of renal clearance determinations, insofar as it is inspired by the aim of minimizing the error of estimating V/t, is superfluous. In determining PhRI, it is unnecessary to clock the urine samples, multiple clearance periods are less important, water loading is unnecessary, urine volumes need not be measured, and finally, catheterization of the urinary bladder serves no useful purpose and should not be undertaken. Indeed, it is necessary only to measure the concentration of phosphorus and creatinine in the serum and urine of a suitably prepared subject, though we have thought it best to adhere to a standardized time of day and to examine two samples of urine and plasma in order to uncover any possible analytical error. The procedure thus becomes sufficiently simple to permit any physician to make the determination in his office provided he can have the chemical analyses performed.

The sole advantage of the conventional procedure is that C_{Cr} can then be determined, and is yielded as an intermediary value in the course of the conventional calculation of PhRI. The interpretation to be placed upon PhRI might theoretically be affected by knowledge of the exact value for C_{Cr}, in that when GFR has fallen sufficiently, the concentration of serum phosphorus will tend to rise and in consequence the parathyroid glands may become overactive, causing PhRI to be depressed. This consideration will hardly arise, however, unless the serum phosphorus concentration is elevated or at least high-normal and azotemia is present, both of which facts will transpire when the concentration data are examined; and under these circumstances especially, C_{Cr} does not provide a very accurate means for estimation of GFR. It should be noted, however, that the considerable error of estimating GFR as C_{Cr} is reflected only to a very limited extent in the absolute value for PhRI, because of the low values generally found

for C_{Ph}/C_{Cr}. If, for example, the value for C_{Cr} deviates by 10 per cent from the actual value of GFR, the index calculated as $1-C_{Ph}/C_{Cr}$ will differ by by .01 or less from $1-C_{Ph}/GFR$ throughout the normal range of PhRI.

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A COMPACT APPARATUS FOR ASCENDING PAPER CHROMATOGRAPHY

To the Editor:

A compact apparatus for ascending chromatography has been devised in this laboratory and successfully used during the past year to separate and measure various steroids in the blood and urine. The apparatus (Fig. 1) consists of a stainless-steel paper holder, $22\frac{5}{8}$ inches high and $3\frac{3}{4}$ inches in diameter, for use in a Pyrex hydrometer jar (Corning #2962, $4\frac{1}{2}$ inches outside diameter, without spout). The holder is designed to accommodate a chromatogram $9\frac{1}{8}\times22\frac{1}{2}$ inches, *i.e.*, half the width of the standard large sheet of Whatman filter-paper. The paper chromatogram is inserted through the top of the holder into the base-plate, which serves as the solvent trough, and is fastened to the top ring with stainless-steel clips. The wire struts connecting the two supporting rods hold the free edges of the chromatogram in place, without interfering with solvent flow. Near the lower end of the hollow center-rod is a receptacle which holds a small amount of the mobile phase for equilibration purposes; this feeds a narrow

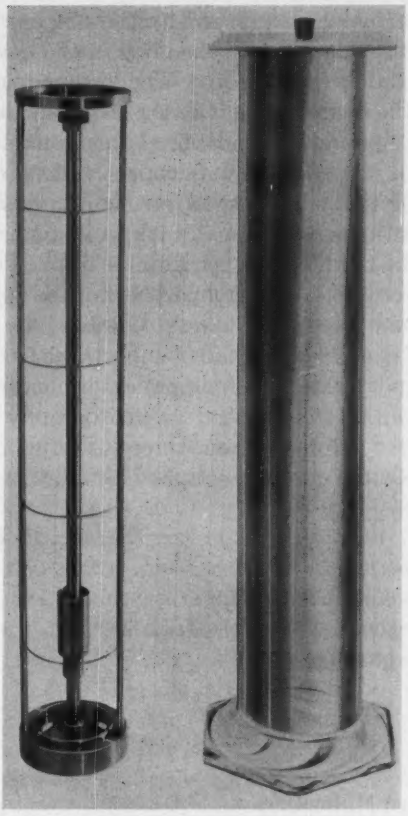

FIG. 1. Compact apparatus for ascending paper chromatography.

cylinder of paper slipped into it over the center rod. The removable nut at the top of this rod functions as a handle.

The chromatogram is conveniently spotted after insertion into the paper holder. A 10–15 ml. portion of the mobile phase is then dripped down the paper cylinder into the small center receptacle. The tank is prepared by plastering a lining sheet of filter paper to the wall with 50–60 ml. of the stationary solvent phase and decanting the excess which accumulates at the bottom. The paper holder is gently lowered into the tank, which is sealed with a glass lid. After equilibration is achieved, the lid-stopper is briefly removed, a funnel is inserted through the hole into the center rod, 50–60 ml. of the mobile solvent phase is poured through the rod into the base plate, and the stopper is replaced. The progress of ascending chromatography is easily inspected through the glass lid. When chromatography

is finished, the paper holder is grasped by the nut on the center rod and lifted out of the tank. The solvent remaining in the base-plate and center receptacle is aspirated with a pipette. The chromatogram may then be dried, sprayed, and heated while left in the paper holder.

The immediately apparent advantage of this apparatus over the usual assembly is its small size but adequate capacity. As a result, paper partition chromatography may be carried out under conditions difficult to achieve with conventional assemblies, such as in a small hood when noxious solvents must be used, or in a refrigerator or oven when unusual temperature ranges are required. The compactness of the apparatus, which can be picked up with one hand, results in portability, simplicity in cleaning, and conservation of storage space—all of importance to the routine hospital laboratory. The paper holder itself simplifies chromatography by making it possible to carry out all the essential chromatography steps with minimal handling of the paper chromatogram. Once the paper is inserted into the holder it may be spotted, chromatographed, dried, sprayed, and heated *in situ*.

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Acknowledgment

The author wishes to acknowledge the technical assistance of John Migliore and the encouragement of Alfred M. Bongiovanni, M.D.

Addendum

The apparatus described has recently been modified to permit its use for either ascending or descending chromatography. Details of construction will be furnished upon request.

LACK OF PLASMA CORTISOL AND URINARY ALDOSTERONE IN A PREGNANT WOMAN WITH ADDISON'S DISEASE

TO THE EDITOR:

The concentration of free plasma 17-hydroxycorticosteroids (mainly cortisol) increases during normal pregnancy (1–2). However, the lack of total 17-hydroxysteroids in the urine of a pregnant Addisonian led us to

suggest that these compounds are not produced by the placenta (3). This opinion is supported by the fact that the level of urinary Porter-Silber chromogens and formaldehydogenic substances (measured after enzymatic hydrolysis) is constant during normal pregnancy (4). The recent isolation by Berliner *et al.* of cortisol and related metabolites from placenta (5) has again drawn attention to the placental biogenesis of cortisol.

We have studied a new case of pregnancy in a woman with Addison's disease, using improved methods, and have found neither plasma nor urinary cortisol.

Mrs. P., 22 years old, was 148.0 cm. tall. She had had Addison's disease for six years when she became pregnant. She was delivered in the fortieth week of a normal female child, weighing 1,550 Gm. (the mother's birthweight was 1,500 Gm.).

Cortisol

Two plasma samples were studied: the first (30 ml.) was taken in the thirty-sixth week, when the patient was receiving 150 μg. of 9α-fluorocortisol per day; the second (45 ml.) was taken in the thirty-eighth week when the treatment was 2.5 mg. of desoxycorticosterone per day. In both instances the plasma was separated from the blood cells at once, and was extracted by chloroform. The extracts were washed with Na_2CO_3 and water and evaporated to dryness. The first extract was kept in a refrigerator until the second had been prepared in the same manner. Both extracts were then pooled and chromatographed on a Florisil column and on paper to isolate cortisol, but no trace of it was found.

Plasma samples from normal pregnant women (in the twenty-eighth to thirty-eighth weeks of pregnancy) were prepared in exactly the same manner. The amounts of cortisol found were never less than 8 μg. per 100 ml. (range, 8 to 32 μg.). We can therefore assume that there was less than 0.5 μg. of cortisol per 100 ml. of plasma in the patient with Addison's disease.

Moreover we have found neither cortisol nor cortisone in the urine of this patient, whereas these compounds were present in the urine of the normal pregnant women (at the same period of pregnancy) in definitely increased quantities compared with nonpregnant women.

It appears that the increased concentration of free 17-hydroxysteroids in the plasma during normal pregnancy is not derived from the placenta.

Aldosterone

The excretion of aldosterone is increased during normal pregnancy (6, 7) and Berliner *et al.* (5) have isolated aldosterone from placenta (3 μg./Kg.). These facts may lead one to assume that the placenta secretes aldosterone.

The excretion of aldosterone in Mrs. P. was studied during the eight-

eenth, thirty-fourth and thirty-sixth weeks of pregnancy. She was receiving at the time either small quantities of 9α-fluorocortisol or nothing (Table 1), and the sodium and potassium intakes were grossly normal.

The urine was subjected to hydrolysis at pH 1 for twenty-four hours at room temperature and extracted by chloroform; then hydrolysis was carried out with β-glucuronidase and extraction was repeated. In the thirty-fourth week of pregnancy, hydrolysis was conducted in the reverse manner —first with glucuronidase and then with acid (pH 1). Our technique for the physico-chemical determination of aldosterone is very similar to that of Neher and Wettstein (14) but the chloroform extracts are submitted to a benzene-water partition. Two 24-hour samples of urine (eighteenth and thirty-sixth weeks) and one 12-hour sample (thirty-fourth week) were tested. We were unable to detect any trace of aldosterone.

Under the same dietary and technical conditions, we found a definitely

TABLE 1. URINARY STEROIDS OF A PREGNANT WOMAN WITH ADDISON'S DISEASE

	Treatment* (mg./day)	Urinary steroids (mg./24 hrs.)†									
		17-KS [1]	17-OH [2]	F.S. [3]	D.N.P.H. [4]	R.S.‡ [5]	P.G. [6]	P.S. [7]	Cortisol [8]	Cortisone [9]	Aldosterone [10]
Before pregnancy	40.0 mg. F	2.6	0.5	—	16.2	—	—	trace	—	—	—
Week of pregnancy§											
18	0.10 mg. FF	3.0	2.3	—	1.7	—	7.2	0.08	0	0	0
34	None‖	4.5	2.8	2.7	9.6	13.2	17.9	1.28	0	0	0
36	0.15 mg. FF	1.8¶	1.5¶	4.9¶	—	10.6¶	15.0¶	2.00¶	0	0	0
38	2.5 mg. DOC	1.8♯	1.4♯	4.2♯	—	7.6♯	—	—	—	—	—
Sixth week after delivery	0.20 mg. FF	2.8	2.9	—	trace	—	trace	trace	0	0	—

*F = Cortisol by mouth.
FF = 9α-Fluorocortisol by mouth.
DOC = Desoxycorticosterone acetate intramuscularly.

† [1] 17-Ketosteroids; hot-acid hydrolysis, Zimmermann chromogen.
[2] 17-Hydroxycorticoids; enzymatic hydrolysis, Silber-Porter technic (8).
[3] Formaldehydogenic substances; enzymatic hydrolysis, Desgrez technic (9).
[4] "2-4-Dinitrophenylhydrazine corticoids"; enzymatic hydrolysis, Gornall-MacDonald reaction (10).
[5] "Reducing lipids"; enzymatic hydrolysis, phosphotungstomolybdic reagent (11).
[6] Pregnanediol; enzymatic hydrolysis, Astwood purification-Talbot reagent, Crepy technic (12).
[7] Phenolsteroids (estrogens); enzymatic hydrolysis, Kober reaction, Jayle technic (13).
[8] Cortisol; hydrolysis at pH 1, quantitative paper chromatographic method.
[9] Cortisone; hydrolysis at pH 1, quantitative paper chromatographic method.
[10] Aldosterone (see text).

‡ The three values for reducing substances are definitely greater than in the nonpregnant Addisonian receiving the same treatment, but the decrease from the 34th to the 38th week is at variance with the increase observed in normal pregnant women at the same period of pregnancy. This may be related to the insufficient size of the uterus-placenta at that stage.

§ The week from the first day of the last menstrual period.
‖ Cortisol (20 mg./day) stopped 48 hrs. previously.
¶ From pooled urines of weeks 34–38.
♯ From pooled urines of weeks 38–39.

high excretion of aldosterone in a normal pregnant woman. We suggest therefore that aldosterone is not produced by the placenta, and that the findings of Berliner and associates may be due to placental protein adsorption or to a "specific concentrating mechanism" (15).

The classic interpretation of gravidic hypercorticism does not provide a satisfactory explanation of the contrast between the normal gravidic increases in plasma and urinary cortisol and urinary aldosterone and the constant level of the hydrogenated metabolites (Porter-Silber chromogens and formaldehydogenic substances). Rather, we suggest a defect in hepatic steroid catabolism (hydrogenation and conjugation) due to the high level of hormones in pregnancy.

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EXCRETION OF PREGNANE-3α,17α,20α-TRIOL IN PREGNANCY*†

TO THE EDITOR:

Data have been presented to establish pregnane-3α,17α,20α-triol (hereafter referred to as pregnanetriol) as a urinary metabolite of 17α-hydroxyprogesterone (1, 2). 17α-Hydroxyprogesterone has been shown to be a precursor of cortisone and hydrocortisone in adrenal steroid biosynthesis (3, 4). Slaunwhite and Samuels (5) reported the conversion of progesterone to 17α-hydroxyprogesterone to androstenedione in testis homogenates, and Solomon, Van de Wiele and Lieberman (6) were able to demonstrate a similar conversion in bovine ovarian homogenates. Further evidence is available to indicate that testosterone may serve as a precursor to estrogen (7–9). Thus 17α-hydroxyprogesterone constitutes an important intermediary in the biosynthesis of both adrenal and gonadal steroids. Although no accurate data are available indicating the conversion rate of 17α-hydroxyprogesterone to pregnanetriol, one may assume that within certain limits increased urinary pregnanetriol excretion reflects increased adrenal activity and perhaps also increased conversion of progesterone to androgens and/or estrogens.

When the plan of this study was conceived, we were not aware of the role of the 17α-hydroxyprogesterone in androgen and estrogen synthesis, but were only interested in establishing further evidence for increased corticoid synthesis in pregnancy. It was primarily the work of Solomon, Van de Wiele and Lieberman that made us reconsider the interpretation of our findings.

METHODS AND RESULTS

Urine was collected at regular intervals from 10 patients with uncomplicated pregnancies in the second and third trimester; in 6 of these, urine was

* Presented at the Thirty-ninth Annual Meeting of The Endocrine Society, New York, N. Y., May 30–June 1, 1957.

† This work was supported by a grant (EDC 43) from the American Cancer Society.

also collected on the first and second postpartum day. Ten normal nonpregnant women of childbearing age served as controls.

The method used for the determination of pregnanetriol has been described in an earlier paper (10). It includes beta-glucuronidase hydrolysis, ether extraction and chromatography on Florisil. Quantitation was carried out following oxidation of pregnanetriol to etiocholanolone with bismuthate. The identity of pregnanetriol was established by obtaining its spectrum in sulfuric acid and its infrared spectrum following acetylation. All determinations were carried out on aliquots from 24-hour urine samples.

Results. The values for the nonpregnant control group agreed with those reported by Bongiovanni (11) and varied from <0.1 mg. to 1.6 mg. per twenty-four hours, with a mean of 1.1 mg. During pregnancy there was a rise in the last trimester. The highest excretions occurred in the tenth month and ranged from 3.4 to 7.2 mg. per twenty-four hours, with a mean of 5 mg. Immediately following delivery, the excretion of pregnanetriol returned to the levels observed in the nonpregnant women (Fig. 1).

Since there is evidence, though partly indirect, that the placenta and adrenals are capable of carrying out 17-hydroxylation of progesterone (12, 13), both organs may be considered as the source of precursor of pregnanetriol. The sudden drop in pregnanetriol excretion following delivery suggests the removal of the source rather than the decreasing secretion of a previously stimulated or hyperplastic adrenal gland. In order to investigate this further, we obtained urine specimens from a pregnant woman

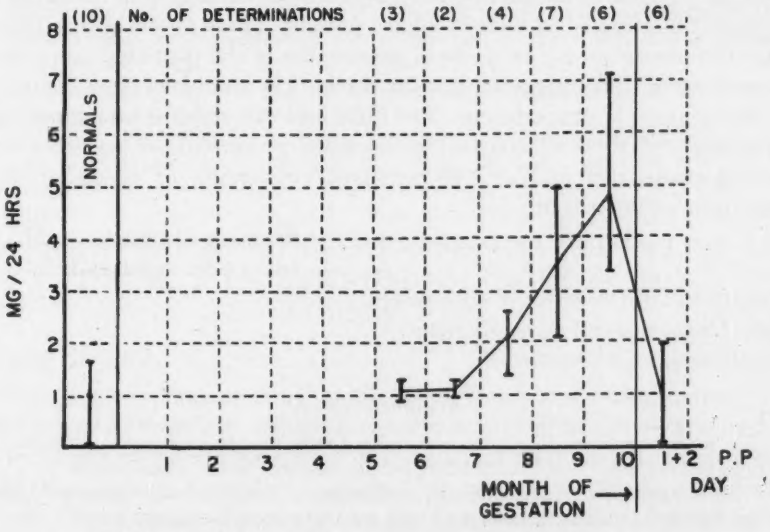

FIG. 1. Urinary excretion of pregnanetriol in pregnancy.

who had undergone bilateral total adrenalectomy for Cushing's disease six months before this pregnancy.

In the eighth month of pregnancy, urine was collected over a period of one week and stored under refrigeration. An amount measuring approximately 3 liters was adjusted to pH 4.5 with acetic acid and incubated with buffer (1/10 volume, sodium acetate, pH 4.5) and beta-glucuronidase (300 units per ml. at 37° for seventy-two hours). The urine was extracted with 4 volumes of ethyl acetate and then discarded. The extract was washed with 0.1 *N* sodium hydroxide until pigment-free, and then with small amounts of water until neutral. Fractional chromatography on Florisil was carried out as described earlier, and the 4 per cent fraction was rechromatographed three times. Identification was attempted at this point by obtaining a spectrum in concentrated sulfuric acid. This resembled closely the spectrum of authentic pregnanetriol with a peak at 440 mμ. Another aliquot was oxidized with bismuthate and a distinct Zimmermann color with maximum absorption at 520 mμ was obtained. Based on this reading, the amount excreted was calculated as 1.4 mg. per twenty-four hours—in the range found in the eighth month of pregnancy in normal patients.

SUMMARY

It has been demonstrated that there is a rise in the urinary levels of pregnanetriol in the last trimester of pregnancy, and that following delivery there is an immediate return to the levels found in nonpregnant women. Pregnanetriol has also been isolated and identified in the urine of a pregnant bilaterally adrenalectomized patient. These observations indicate that the placenta may be a site of production of the probable precursor of pregnanetriol. This suggests that the placenta is capable of carrying out 17-hydroxylation of progesterone. The increased excretion of pregnanetriol in pregnancy may be related to the increased production of corticosteroids during pregnancy and/or the increased conversion of progesterone to androgen and estrogen.

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Acknowledgment

The authors wish to thank Doctor P. K. Bondy for his constructive criticism and encouragement, and Miss Muriel Shorr for her valuable technical assistance.

Pure samples of pregnanetriol and pregnanetriol diacetate were obtained through the generosity of Doctor S. Lieberman and Doctor A. Bongiovanni.

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A CLINICAL SYNDROME ASSOCIATED WITH A DEFECT IN STEROID GLUCURONIDE FORMATION

To the Editor:

There is general agreement that the major fraction of endogenously produced adrenal steroids is rapidly and essentially completely metabolized in the body and excreted in the urine as conjugated products. It is also recognized that, in man, the major fraction of the numerous corticosteroid and 17-ketosteroid metabolites appearing in the urine is conjugated with glu-

curonic acid. Following the administration of hydrocortisone-4-C^{14}, approximately 60 per cent of the excreted radioactivity appears as metabolites conjugated with glucuronic acid (1). Isselbacher and Axelrod demonstrated that glucuronides of tetrahydrocortisone (one of the major metabolites of hydrocortisone) as well as of other 3α-ol ring-A saturated steroids could be synthesized *in vitro* by an enzyme system present in liver microsomes which transfers glucuronic acid from uridine diphosphate glucuronic acid to the steroids and to other aglycones (2).

It has recently been reported that bilirubin is excreted in the bile as a glucuronide (3, 4). The biosynthesis of bilirubin glucuronide in the liver has been shown to be catalyzed by a microsomal enzyme system similar to that involved in glucuronide formation of steroids (5). The conversion of water-insoluble bilirubin to the more water-soluble bilirubin glucuronide appears to be essential for its excretion in the bile (6). A defect in the hepatic enzyme system involved in the conversion of water-insoluble bilirubin to its water-soluble conjugate would be expected to result in impaired excretion of bile pigment and hence to retention of nonconjugated bilirubin in the plasma (7). It has been suggested (7) that such a defect may be present in congenital nonhemolytic nonobstructive jaundice, a syndrome first described by Crigler and Najjar (8). This syndrome is characterized by persistent jaundice with only indirect-reacting bilirubin in the serum. The excretion of bilirubin in the bile and of urobilinogen in the feces is greatly impaired, although biliary excretion is not affected otherwise (7), and there is no increased hemolysis.

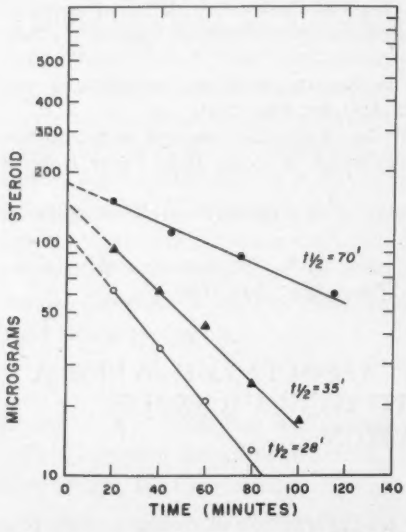

FIG. 1. Disappearance of tetrahydrohydrocortisone from plasma following intravenous administration. ● = Patient J.D.; ▲ = Patients with cirrhosis; ○ = Normal subjects. (Plasma steroid levels as μg./100 ml.)

It has been shown that in patients with this syndrome the rate and magnitude of the formation of glucuronides of compounds other than bilirubin are also impaired (9). It was therefore of interest to determine whether the conjugation of steroids with glucuronic acid is impaired in such patients.

J.D., the subject of the present study, was a 7-year-old boy with severe congenital nonhemolytic jaun-

dice. The plasma level of nonconjugated bilirubin was 30 mg. per 100 ml., and there was no bilirubinuria (10). Figure 1 shows the rate of disappearance of tetrahydrohydrocortisone from the plasma following a five-minute infusion of approximately 1 mg. per kilo of body weight. Disappearance was significantly delayed when compared to that observed in 4 normal subjects, or in 3 patients with liver disease (2 with cirrhosis and 1 with hepatitis).

The present patient (J.D.) had a normal plasma level of hydrocortisone (12 μg. per 100 ml.), as determined by the phenylhydrazine and isotope

TABLE 1. FREE AND CONJUGATED URINARY STEROIDS FOLLOWING INTRAVENOUS ADMINISTRATION OF HYDROCORTISONE-4-C^{14}

Subject	Dose administered		Per cent excreted in 24 hours					
			Free steroids		Conjugated steroids			
					Glucuronide		Butanol-soluble	
	PNH*	C^{14}	PNH	C^{14}	PNH	C^{14}	PNH	C^{14}
J.D.	100 mg.	1.1 μc.	5	6	10	13	22	69
M.P. (control)	100 mg.	1.1 μc.	6	9	20†	42	23	76

* PNH = phenylhydrazine-reacting, by colorimetric determination.

† Additional studies in other normal control subjects have demonstrated that between 25 and 30 per cent of the urinary metabolites of hydrocortisone are present as phenylhydrazine-reacting steroids after glucuronidase hydrolysis.

dilution assay methods (11), and there was no defect in his ability to metabolize 100 mg. of hydrocortisone[1] infused intravenously (biologic half-time, ninety-six minutes). However, the metabolites of hydrocortisone conjugated with glucuronic acid appeared in the plasma at a much slower rate than in normal subjects. Furthermore, the fraction of glucuronic acid-conjugated metabolites appearing in the urine after infusion of hydrocortisone was only about half of that found in normal subjects (Table 1).

These results indicate that in congenital nonhemolytic jaundice, the rate of steroid glucuronide formation is greatly reduced, but the ability to form glucuronides is not entirely abolished. On the other hand, bilirubin glucuronide can not be detected in the plasma, bile or urine (7). It is also

[1] Hydrocortisone is not conjugated with glucuronic acid because it lacks the 3α-ol function in ring A (2). The rate of disappearance of tetrahydrohydrocortisone from the plasma, however, is presumably in large measure a reflection of the capacity of the liver to conjugate this steroid with glucuronic acid (2, 12).

of interest that even though the formation of steroid glucuronides is impaired, other mechanisms capable of forming highly water-soluble steroid metabolites are not affected. The metabolism of endogenously produced biologically active steroids is apparently not disturbed, and the defect in steroid glucuronide formation can be demonstrated only by administration of a loading dose of ring A-reduced steroids.

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THE ISOLATION OF MYOGLOBIN IN PROGRESSIVE MUSCULAR DYSTROPHY*

TO THE EDITOR:

Pallor of the skeletal muscle in muscular dystrophy has been recognized for many years (1). We have observed that muscle is very pale early in the course of this disorder, at a time when clinical disability is barely perceptible (2). Myoglobin levels have been measured in muscle from patients with relatively advanced muscular dystrophy by Biorck (3) and others, who estimated myoglobin concentration in muscle extracts containing both hemoglobin and myoglobin on the basis of the slight spectral differences between these two compounds. These studies showed markedly lowered myoglobin values in extracts from dystrophic muscle as compared to extracts from normal muscle.

Although normal human myoglobin has been carefully characterized (4–6), the isolation of myoglobin from dystrophic human muscle has not been reported. We have examined several samples of dystrophic muscle in our laboratory, but in most of these myoglobin was either not detectable or was present in such small amounts that our attempts at isolation of the myoglobin failed. However, it has been possible to isolate myoglobin from the psoas muscle of a patient with the myotonic form of progressive muscular dystrophy and to compare its electrophoretic characteristics with those of myoglobin from a normal human subject.

METHOD

Myoglobin was prepared by the method of Drabkin (7) as modified by Ginger *et al.* (8) from psoas, iliopsoas and pectoralis muscles obtained at autopsy from patients who died of diseases other than primary disorders of the nerves or muscles, and from the psoas muscle of a patient with myotonic dystrophy. By this technique, hemoglobin is precipitated in the presence of 3 *M* phosphate buffer at pH 6.6, while the myoglobin remains in solution. The final product is dialyzed against water until it is free of phosphate and is then concentrated by lyophilization for storage, or by ultracentrifugation or evaporation for immediate electrophoresis. Complete removal of hemoglobin by this technique can be demonstrated by isolating myoglobin free of radioactivity from muscle samples contaminated with Fe^{59}-labelled hemoglobin. The myoglobins were subjected to electrophoresis on paper for eighteen hours in a Spinco strip electrophoresis apparatus using 0.1 *M* barbital buffer at pH 8.5, followed by staining with bromphenol blue. Free electrophoresis was performed on the isolated myoglobins in a standard Tiselius apparatus using the same buffer system. In addition, in order to eliminate any possibility that the mobilities of the myoglobins were altered by phosphate treatment, lyophilization or

* This work was supported by research grants from the Muscular Dystrophy Associations of America, Incorporated, and the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, United States Public Health Service.

concentration, crude aqueous extracts of normal and dystrophic muscles were prepared and electrophoresed on paper without further treatment. The electrophorograms were then analyzed in the Spinco analytrol.

RESULTS AND DISCUSSION

Representative paper electrophoreses are shown in Figure 1. In each instance hemoglobin had a greater mobility than myoglobin, whereas myoglobin from dystrophic muscle had the same mobility as that from normal muscles (several samples). In the electrophorograms of isolated, concentrated myoglobin and of crude aqueous extracts, the analytrol tracing showed the myoglobin to be 11 mm. from the origin. In this system, hemoglobin migrates 26 mm. Apparently, the isolation and concentration procedures did not influence the electrophoretic mobility of the myoglobins. Paper electrophoresis of a crude aqueous preparation of heart muscle from a patient with childhood progressive muscular dystrophy showed the myoglobin band to be 10 mm. from the origin—essentially the same position as in the other myoglobin samples, whether from skeletal or cardiac muscle.

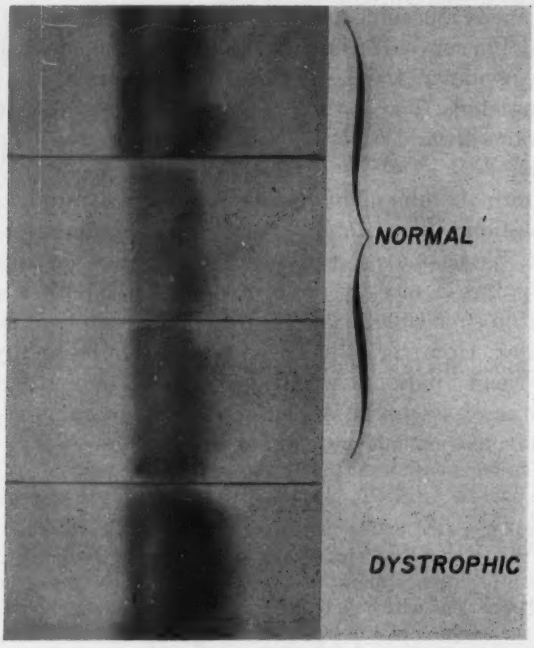

FIG. 1. Representative paper electrophoreses of myoglobin from the muscles of 3 normal subjects compared to that from a patient with myotonic dystrophy. Note the similarity in electrophoretic mobility of the 4 samples.

Free electrophoresis of the myoglobins confirmed the results obtained with paper electrophoresis. The values for normal myoglobin were: major component (two separate preparations), 2.4 and 2.8 $\mu \times 10^{-5}$, with minor peaks at 1.6 and 3.6 $\mu \times 10^{-5}$. The results with myoglobin from dystrophic muscle were: a major peak with a mobility of 2.4 $\mu \times 10^{-5}$ on free electrophoresis, and a minor peak with a mobility of 1.2 $\mu \times 10^{-5}$.

The observation that the muscle becomes pale in progressive muscular dystrophy before serious clinical disability is apparent suggested to us that the various forms of this disease might be associated with genetically determined abnormalities of myoglobin similar to those now known to occur in hemoglobin in certain hereditary anemias. The present studies, which reveal only a quantitative and no qualitative defect in myoglobin in muscular dystrophy, fail to support this hypothesis. However, additional studies will have to be made before it can be stated with assurance that myoglobin in all forms of this disease is not electrophoretically abnormal. In addition, other techniques for the characterization of protein need to be applied to the isolated myoglobin before it can be concluded that the protein is structurally normal.

Other explanations for the decrease in myoglobin content of the muscle in progressive muscular dystrophy might be that this disorder is associated with abnormal synthesis or excessive destruction of this important heme protein. Still another explanation for the decreased myoglobin content of dystrophic muscle is possible. The muscle in progressive muscular dystrophy exhibits many of the histologic findings characteristic of the reaction to injury (9). It is possible that the low content of myoglobin is the result of escape of this pigment from the diseased muscle. The apparent early decrease of myoglobin in the muscle in muscular dystrophy suggests that one of the first two of these alternatives is the more likely explanation.

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The Endocrine Society

THE 1958 ANNUAL MEETING

The Fortieth Annual Meeting of The Endocrine Society will be held in the St. Francis Hotel, San Francisco, California, Thursday, Friday and Saturday, *June 19, 20, and 21, 1958.*

The Committee on Local Arrangements—Dr. Roberto Escamilla, Chairman; Dr. Donald E. Bernstein, Dr. Peter H. Forsham, Dr. Minnie B. Goldberg, Dr. Gilbert S. Gordan, Dr. Francis S. Greenspan, Dr. C. H. Li, as members of the committee.

All Scientific Sessions will be held from 9:00 A.M. to 5:00 P.M. daily in the Colonial Ballroom, and in addition there will be simultaneous afternoon sessions in the Italian Room. The annual dinner is scheduled for Friday, June 20 at 7:30 P.M., preceded by cocktails at 6:30 P.M.

All reservations for rooms must be made through the AMA Housing Bureau, c/o Convention and Tourist Bureau, Civic Auditorium, San Francisco, California, after January 1, 1958. No reservations will be accepted before that date. If possible, official application forms as published in the Journal of the American Medical Association should be used. Arrival and departure dates must be stated.

Final program, membership card and advance registration forms will be sent on May 15, 1958 to members whose current dues have been paid.

Those wishing to present papers, which will be strictly limited to ten minutes, should send four copies of the title and abstract to the Vice-President, Dr. Rulon W. Rawson, 444 E. 68th St., New York 21, N. Y., not later than *February 1, 1958. It is imperative that the abstracts be informative and complete with results and conclusions—not a statement that those will be presented at the meeting*—in order that they may be of reference value and suitable for printing in the program. The following regulations for the preparation of abstracts and titles must be carefully followed to insure consideration of the paper for the program:

1. Abstracts may not exceed two hundred words, or equivalent space, exclusive of title. No footnotes or acknowledgments to sponsors can be published. Reference, if used, must be placed in the body of the text. The abstract should consist of a single paragraph, if possible. Structural chemical formulas cannot be used.

2. The title heading must be arranged as follows:

   Line 1. Title, not to exceed fifteen words;

Line 2. Author/s. The name of each nonmember-author collaborating with member-authors is to be followed by the phrase "(by invitation)." Names of nonmembers who are introduced, *i.e.*, who are not collaborators with member-authors, are to be followed by the phrase "(introduced by . . .)." The principal degree, *e.g.*, M.D., of each author should be written after his name.

Line 3. Institution of origin and city in which institution is located.

3. The body of the abstract, typed double-space, should follow the heading. The original copy should be on bond paper. There should be three copies.
4. Abstracts should be letter perfect, since there will be no opportunity for proofreading by the authors.

THE 1958 AWARDS

The selection of the recipients of the awards of The Endocrine Society is made by a Committee appointed by the Council of the Society. These awards and fellowships carry no obligation by the recipient to the Society or to the donors.

MEDAL OF THE ENDOCRINE SOCIETY

In 1954 the Council of the Society voted to establish a medal and an honorarium of $1,000 to be given to an individual for work of special distinction in endocrinology. The recipient shall be chosen from nominations presented by members of the Society and is limited to citizens of the United States and Canada. Dr. Carl R. Moore was the recipient in 1955, Dr. Frederick L. Hisaw in 1956, and Dr. Joseph C. Aub in 1957.

THE CIBA AWARD

The Ciba Award, to recognize the meritorious accomplishments of an investigator not more than 35 years of age in the field of clinical or preclinica endocrinology, was established in 1942, but no recipient was selected in 1942 or 1943. In 1944 the Award was presented to Dr. E. B. Astwood; 1945—Dr. Jane A. Russell; 1946—Dr. Martin M. Hoffman; 1947—Dr. Choh Hao Li; 1948—Dr. Carl Heller; 1949—Dr. George Sayers; 1950—Dr. Oscar M. Hechter; 1951—Dr. Albert Segaloff; 1952—Dr. Seymour Lieberman; 1953—Dr. Sidney Roberts and Dr. Clara Szego (Mrs. Roberts); 1954—Dr. Isadore M. Rosenberg; 1955—Dr. Jack Gross; 1956—

Dr. Alfred M. Bongiovanni; 1957—Dr. Nicholas S. Halmi. Prior to 1952 the Award was $1,200. It is now $1,800. If within twenty-four months of the date of the award, the recipient should choose to use it toward further study in a laboratory other than that in which he is at present working, it will be increased to $2,500.

THE AYERST AND THE SQUIBB FELLOWSHIPS

The Ayerst Fellowship was established in 1947 and the Squibb Fellowship in 1956. They are designed to assist men or women of exceptional promise in furthering their advancement towards a career in endocrinology. Each Fellowship is awarded on alternate years and the stipend, which will not exceed $5,000, may be divided into two Fellowships in varying amounts in accordance with the qualifications of the appointees. Individuals possessing the M.D. or Ph.D. degree, or candidates for either of these degrees, are eligible for appointment.

Applicants must submit the following information:

1. Evidence of scientific ability as attested by studies completed or in progress.
2. Recommendations from individuals familiar with the candidate and his work.
3. A proposed program of study.
4. Acceptance of the individual by the head of the department in which the Fellowship will be held.
5. A statement that he or she will serve full time if awarded a Fellowship. A small amount of time (10 to 15 per cent) may be spent in course work or participation in teaching, the latter purely on a voluntary basis.

THE SCHERING AND THE UPJOHN SCHOLARS OF THE ENDOCRINE SOCIETY

The Council of The Endocrine Society has established a category of Scholars. These grants have been made available through the generosity of the Schering Corporation and the Upjohn Company, and will be awarded to established investigators and teachers in the field of endocrinology who wish to extend their opportunities for work either in this country or abroad.

The awards will not exceed $2,500 annually for each individual and will be granted on the basis of proposals submitted by the applicant. Such applications should include the estimated financial needs. The funds may be used for travel, maintenance and other expenses.

Nominations

Nominations for the Medal of the Endocrine Society; the Ciba Award; and the Ayerst and the Squibb Fellowships may be made by any member of The Endocrine Society. They should be submitted on forms which may be obtained from the Office of the Secretary, 1200 North Walker Street, Oklahoma City 3, Oklahoma. Completed nominations should be returned to the Secretary not later than *November 1* each year.

Proposals for appointments as Scholars of The Endocrine Society should be made in writing by the individual, and addressed to the Secretary of the Society. They should be submitted by *November 1* each year.

The Awards Committee will meet in November and notice of awards to successful nominees and applicants will be made not later than December 1.

The American Goiter Association

THE 1958 ANNUAL MEETING

The next Annual Meeting of The American Goiter Association will be held in the St. Francis Hotel, San Francisco, California, on *June 17, 18 and 19, 1958.*

THE VAN METER PRIZE AWARD FOR 1958

The American Goiter Association again offers the Van Meter Prize Award of $300.00 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The award will be made at the annual meeting of the Association, which will be held in the St. Francis Hotel, San Francisco, California, June 17, 18 and 19, 1958, provided essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations, should not exceed 3,000 words in length and must be presented in English. Duplicate typewritten copies, double spaced, should be sent to the Secretary, Dr. John C. McClintock, 149½ Washington Avenue, Albany 10, N. Y., *not later than February 1, 1958.* The committee who will review the manuscripts is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for the presentation of the winning essay by the author if it is possible for him to attend.

SECOND WORLD CONGRESS OF THE INTERNATIONAL FEDERATION OF GYNAECOLOGY AND OBSTETRICS

The International Federation of Gynaecology and Obstetrics was founded in Geneva in 1954 where it held its First World Congress. Meeting every four years, according to its constitution, the International Federation chose Montreal, Canada, as the site of its Second World Congress, from *June 22 to 28, 1958*. All scientific sessions, scientific exhibits and moving pictures will be held in the newly-built Queen Elizabeth Hotel. The main features will be plenary conferences with invited guest speakers, round table discussions, and free communications. Information and registration forms may be obtained by writing to the Montreal Committee, Second World Congress, International Federation of Gynaecology and Obstetrics, 1414 Drummond Street, Suite 220, Montreal 25, Quebec, Canada.

CORRECTION

In the article by Greer, M. A. and Shull, H. F. entitled "A Quantitative Study of the Effect of Thyrotropin upon the Thyroidal Secretion Rate in Euthyroid and Thyrotoxic Subjects" (*J. Clin. Endocrinol. & Metab.* **17**: 1030–1039 (Sept.) 1957) the sentence beginning on line 20 of page 1037 should be changed from "The data (12) indicating that the serum PBI level of thyrotoxic patients is three to five times as high as in euthyroid patients . . . " to "The data (12) indicating that the serum thyrotropin level of thyrotoxic patients is three to five times as high as in euthyroid patients . . . ."

BOOK REGISTER

(*The*) *Biologic Basis of Cancer Management.* By FREDDY HOMBURGER, M.D., Research Professor of Medicine, Tufts University School of Medicine, Boston, and Scientific Associate, Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine. Forewords by LAUREN V. ACKERMAN, M.D., CLARENCE COOK LITTLE, Sc.D. and ALTON OCHSNER, M.D. The subject is treated from the viewpoints of fundamental research, experimental biology, diagnosis, treatment and prevention and provides current information not otherwise published in a single volume. As stated in the Preface, this book relates some of the fundamental knowledge of neoplastic disease and places it in perspective with the clinical problems posed by cancer. It fills the need for an easily readable source of scientific and clinical information and should render it easier for everyone (including medical students, clinicians, research workers and scientists) interested in the field of cancer to acquire knowledge on many phases of cancer research and of the principal public health and clinical problems: 372 pages; 39 tables; 10 figures; 1957. Paul B. Hoeber, Inc., New York, N. Y. Price $10.00.

Klinik der inneren Secretion. By ALEXIS LABHART, with the assistance of G. R. CONSTAM, C. HEDINGER, K. G. OBER, A. PRADER, P. H. ROSSIER, G. TÖNDURY, M. WERNLY and J. ZANDER. Contains 28 chapters covering the various endocrine diseases, well illustrated with 372 figures, partly in color; 1101 pages; 1957. Springer-Verlag, Berlin, Göttingen, Heidelberg. Price DM 99.80.

L'Année endocrinologique. Ninth year. By M. ALBEAUX-FERNET, L. BELLOT, P. BRÉANT, P. BUGARD, J. CHABOT, J. DERIBREUX, M. GELINET and J. D. ROMANI, contains articles reviewing the latest advances in endocrinology in various fields; 237 pages; 1957. Masson & Cie, éditeurs, Paris.

(*The*) *Malabsorption Syndrome.* A Mount Sinai Hospital Monograph edited by DAVID ADLERSBERG, M.D., Associate Attending Physician for Metabolic Diseases, The Mount Sinai Hospital, and Assistant Clinical Professor of Medicine, College of Physicians & Surgeons, Columbia University, New York, with a Foreword by HENRY L. BOCKUS, M.D. This is a presentation of contributions by members of the Staff of Mount Sinai Hospital and two British guests to a Symposium concerned primarily with the primary or idiopathic malabsorption syndrome (including "nontropical sprue" or "idiopathic steatorrhea"), in an attempt to explain the underlying defect; management of the disease is also discussed; 252 pages; illustrated; 1957. Grune & Stratton, New York. Price $5.50.

Methodology of the Study of Ageing. Volume 3 of Ciba Foundation Colloquia on Ageing, edited by G. E. W. WOLSTENHOLME, M.A., B.CH. and CECILIA M. O'CONNOR, B.Sc. This is a collection of papers presented at the Colloquium on Ageing, London, July 1956. A few of the many topics covered are: methodology of the study of intelligence and emotion in ageing; methodological problems in the study of changes in human performance with age; use of inbred strains of animals in experimental gerontology; study of the ageing of cells; methods and limitations in studies of human organ system function; and reactions to standard stimuli at different ages; 212 pages; 47 illustrations; 1957. Little, Brown and Company, Boston. Price $6.50.

Report of the Medical Research Council for the Year 1955–1956. Presented by the Lord President of the Council to Parliament by Command of Her Majesty, May 1957. Included are reports on research policy, various aspects of medical research, and administration; 270 pages; 1957. London, Her Majesty's Stationery Office. Price 9 shillings net.

Steroid Homeostasis, Hypophysis and Tumorigenesis. By PROFESSOR ALEXANDER LIPSCHUTZ, Director, Institute of Experimental Medicine, National Health Service, Santiago, Chile, with Forewords by CHARLES HUGGINS, M.D. and ALEX HADDOW, M.D. The author summarizes the work and ideas of his own school in the field of endocrine carcinogenesis and relates them to the findings of other workers. There is a discussion of the application of various steroids and other experimental procedures in the disturbance of steroid homeostasis, and also of the anti-fibromatic action of many steroids; 100 pages; paper; 1957. W. Heffer & Sons Ltd., Cambridge, England. Price 15 shillings net.

Transactions of the American Goiter Association for 1956. This volume is an outstanding collection of 38 articles by various authorities on the thyroid who took part in the program of the American Goiter Association meeting in Chicago, May 1956. The most recent advances in the clinical and biologic aspects of thyroid disorders are presented, along with informal discussions. The high quality of the work represented in the Transactions is well known; 488 pages; 182 illustrations; 1957. Charles C Thomas, Publisher, Springfield, Illinois. Price $16.75.

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The Journal of

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Official Journal of The Endocrine Society

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DEC 19 1957

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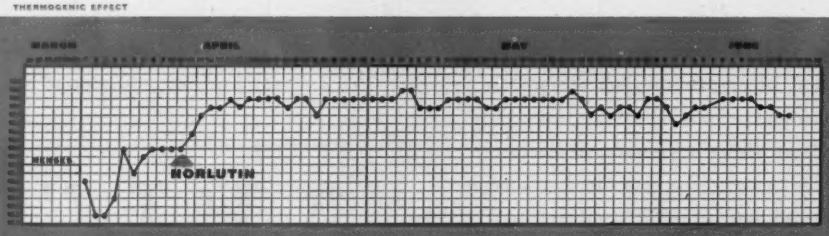

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Entered as second class matter at the Post Office at Springfield, Illinois, and at Menasha, Wisconsin.

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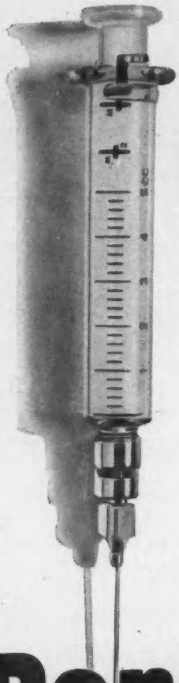

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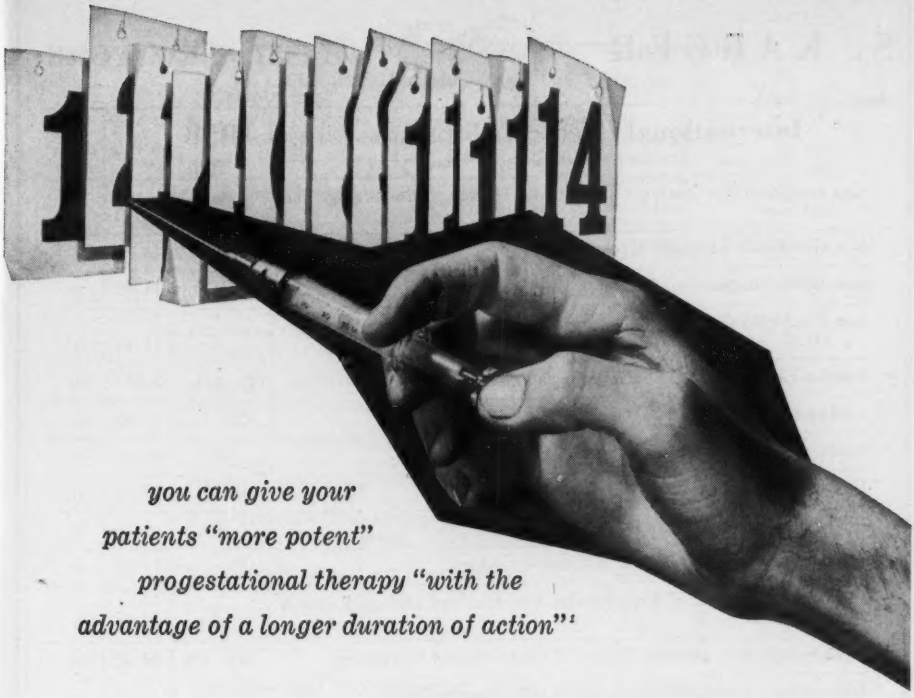

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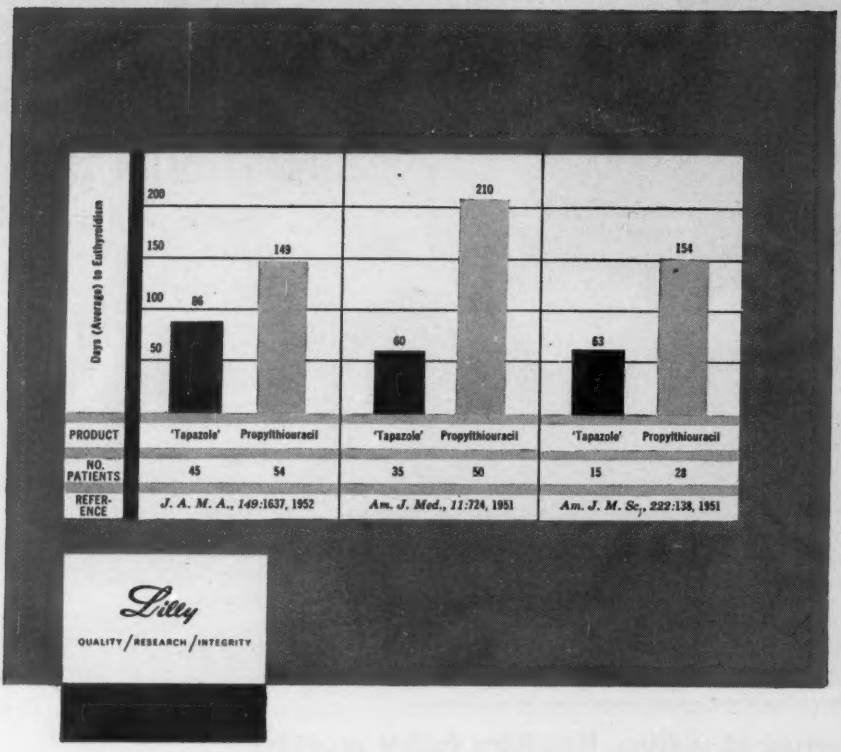

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